EP03/11814

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Signed R. Mahoney

Dated 6 August 2003

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1/77

Request for grant of a patent

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The Patent Office
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1. Your reference — APB [redacted]/DAB/P33108P2

07APR03 E790429 1 D02029
P01/7700 0.00-0308017.3

2. Patent application number
(The Patent Office will fill in his part) — 0308017.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4733587003

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	–
Description	108
Claim(s)	7
Abstract	1
Drawings	–

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	Form 23/77

11. We request the grant of a patent on the basis of this application
Signature Helen Quillin Date 7-Apr-03
HELEN QUILLIN

12. Name and daytime telephone number of person to contact in the United Kingdom: A P Breen 01438 762055

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Notes

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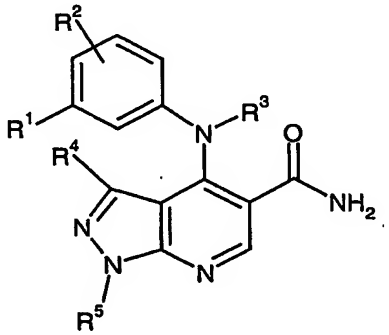
COMPOUNDS

The present invention relates to pyrazolopyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolopyridine compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma or allergic rhinitis.

US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
(Ono)

wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a

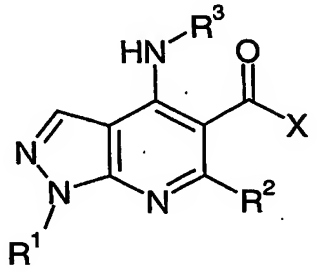
group -$NR^{11}SO_2R^{12}$, 11) a group -$NR^{13}C(O)R^{14}$ or 12) a group -$CH=NR^{15}$. R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4 , methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate is known (ethyl 4-(n-butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate). J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives and their affinities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A1-adenosine receptor ligands.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

The present invention provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



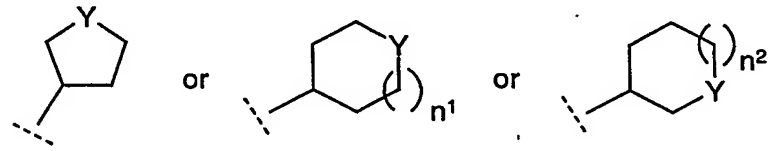
(I)

wherein:

R^1 is a hydrogen atom (H), C_{1-4}alkyl, C_{1-3}fluoroalkyl, $-CH_2CH_2OH$, $-CH_2CH_2CO_2C_{1-2}$alkyl, phenyl or benzyl;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted C_{3-8}cycloalkyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10}; where R^{10} is a hydrogen atom (H), C_{1-4}alkyl (e.g. methyl or ethyl), C_{1-2}fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, or $C(O)$-C_1fluoroalkyl;

and wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy), or C_{1-2}alkyl; and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and X is NR^4R^5 or OR^{5a}, in which:

R^4 is a hydrogen atom (H); C_{1-6}alkyl; C_{1-3}fluoroalkyl; or C_{2-6}alkyl substituted by one substituent R^{11}; and

R^5 is a hydrogen atom (H); C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; or -$(CH_2)_n{}^4$-C_{3-8}cycloalkyl optionally substituted, in the -$(CH_2)_n{}^4$- moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1, 2 or 3;

or R^5 is C_{2-6}alkyl substituted by one or two independent substituents R^{11};

wherein each substituent R^{11}, independently of any other R^{11} substituent present, is: hydroxy (OH); C_{1-6}alkoxy; phenyloxy; benzyloxy; -$NR^{12}R^{13}$; -NR^{15}-C(O)R^{16}; -NR^{15}-C(O)-O-R^{16}; -NR^{15}-C(O)-NH-R^{15}; or -NR^{15}-SO_2R^{16}; and wherein any R^{11} substituent which is OH, alkoxy or -$NR^{12}R^{13}$ is not substituted at any carbon atom, of any R^4 or R^5 substituted alkyl, which is bonded to the nitrogen of NR^4R^5;

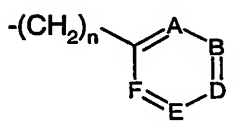
or R^5 is -$(CH_2)_n{}^{11}$-C(O)R^{16}; -$(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$; -CHR^{19}-C(O)$NR^{12}R^{13}$; -$(CH_2)_n{}^{12}$-C(O)OR^{16}; -CHR^{19}-C(O)OR^{16}; -$(CH_2)_n{}^{12}$-SO_2-$NR^{12}R^{13}$; -$(CH_2)_n{}^{12}$-SO_2R^{16}; or -$(CH_2)_n{}^{12}$-CN; wherein n^{11} is 0, 1, 2, 3 or 4 and n^{12} is 1, 2, 3 or 4;

or R^5 is -$(CH_2)_n{}^{13}$-Het wherein n^{13} is 0, 1, 2, 3 or 4 and Het is a 4-, 5-, 6- or 7-membered saturated or partly-saturated heterocyclic ring containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-hetero-atoms present are not bound to the -$(CH_2)_n{}^{13}$- moiety when n^{13} is 1 and are not bound to the nitrogen of NR^4R^5 when n^{13} is 0; wherein any ring-nitrogens which are present and which are not unsaturated (i.e. which do not partake in a double bond) are present as NR^{17} where R^{17} is as defined herein; and wherein one or two of the carbon ring-atoms independently are optionally substituted by C_{1-2}alkyl;

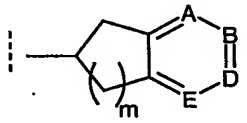
or R^5 is phenyl optionally substituted with one or two of: a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. trifluoromethyl); C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy); C_{1-2}alkylsulphonyl (C_{1-2}alkyl-SO_2-); C_{1-2}alkyl-SO_2-NH-; R^7R^8N-SO_2-; R^7R^8N-CO-; -NR^{15}-C(O)R^{16}; R^7R^8N; OH; C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-SO_2-CH_2-; cyano (CN); or phenyl optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

wherein R^7 and R^8 are independently a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl such as methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two of: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or R^7 and R^8 together are $-(CH_2)_n{}^6-$ or $-C(O)-(CH_2)_n{}^7-$ or $-C(O)-(CH_2)_n{}^7-C(O)-$ or $-(CH_2)_n{}^8-X^7-(CH_2)_n{}^9-$ or $-C(O)-X^7-(CH_2)_n{}^{10}-$ in which: n^6 is 3, 4, 5 or 6, n^7 is 2, 3, 4, or 5 (preferably n^7 is 2, 3 or 4), n^8 and n^9 and n^{10} independently are 2 or 3, and X^7 is O or NR^{14} wherein R^{14} is H or C_{1-2}alkyl;

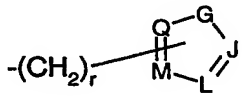
or R^5 has the sub-formula (x), (y) or (z):



(x)



(y)



(z)

wherein in sub-formula (x), n = 1 or 2; in sub-formula (y), m = 1 or 2; and in sub-formula (z), r = 0, 1 or 2;

wherein in sub-formula (x) and (y), none, one or two of A, B, D, E and F are nitrogen; and the remaining of A, B, D, E and F are independently CH or CR^6;

where R^6 is a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-4}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{1-2}alkylsulphonyl (C_{1-2}alkyl-SO_2-); C_{1-2}alkyl-SO_2-NH-; R^7R^8N-SO_2-; R^7R^8N-CO-; $-NR^{15}-C(O)R^{16}$; R^7R^8N; OH; C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-SO_2-CH_2-; cyano (CN); or phenyl optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; wherein R^7 and R^8 are as herein defined;

wherein in sub-formula (z), G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one, two or three of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are independently CH or CR^6 where R^6 is as defined herein;

or R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ or $-C(O)-X^5-(CH_2)_p{}^5-$, in which: p^1 = 3, 4, 5 or 6 (preferably p = 4 or 5), p^2 is 2, 3, 4, or 5 (preferably p^2 is 2, 3 or 4), and p^3 and p^4 and p^5 independently are 2 or 3 (independently preferably 2) and X^5 is O or NR^{17};

wherein R^{17} is a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl; C_{3-6}cycloalkyl; $-(CH_2)_p{}^6-C(O)R^{16}$ wherein p^6 is 0, 1, 2 or 3 (preferably p^6 is 0); $-(CH_2)_p{}^6-C(O)NR^{12}R^{13}$; $-(CH_2)_p{}^6-C(O)OR^{16}$; $-SO_2R^{16}$; or phenyl or benzyl wherein the phenyl or benzyl is optionally substituted at an aromatic carbon atom by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

and wherein, when R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$, the NR^4R^5 heterocycle is optionally substituted by one R^{18} substituent wherein R^{18} is: C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl; C_{3-6}cycloalkyl; C_{1-2}alkoxy (not substituted at a ring-carbon bonded to the NR^4R^5 ring-nitrogen); C_1fluoroalkoxy (not substituted at a ring-carbon bonded to the NR^4R^5 ring-nitrogen); OH (not substituted at a ring-carbon bonded to the NR^4R^5 ring-nitrogen); $-(CH_2)_p{}^7-C(O)R^{16}$ wherein p^7 is 0, 1, 2 or 3 (preferably p^7 is 0 or 1); $-(CH_2)_p{}^7-C(O)OR^{16}$; $-(CH_2)_p{}^7-OC(O)R^{16}$; $-(CH_2)_p{}^7-C(O)NR^{12}R^{13}$; $-(CH_2)_p{}^7-NR^{15}C(O)R^{16}$; $-(CH_2)_p{}^7-NR^{15}C(O)NR^{12}R^{13}$; $-(CH_2)_p{}^7-NR^{15}C(O)OR^{16}$; $-(CH_2)_p{}^7-SO_2R^{16}$; $-(CH_2)_p{}^7-SO_2NR^{12}R^{13}$; $-(CH_2)_p{}^7-NR^{15}SO_2R^{16}$; $-(CH_2)_p{}^7-OH$; $-(CH_2)_p{}^7-OR^{16}$; or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ or $-C(O)-X^5-(CH_2)_p{}^5-$ as defined herein, and wherein the NR^4R^5 heterocycle is fused to a phenyl ring optionally substituted on the phenyl by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; and

R^{5a} is C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl; phenyl optionally substituted with one or two of: a halogen atom, C_{1-2}alkyl, trifluoromethyl, C_{1-2}alkoxy or trifluoromethoxy; or R^{5a} has the sub-formula (x), (y) or (z) as defined herein

and wherein:

R^{12} and R^{13} independently are H; C_{1-5}alkyl (e.g. C_{1-3}alkyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^{12} and R^{13} together are $-(CH_2)_n{}^6-$ or $-C(O)-(CH_2)_n{}^7-$ or $-C(O)-(CH_2)_n{}^7-C(O)-$ or $-(CH_2)_n{}^8-X^{12}-(CH_2)_n{}^9-$ or $-C(O)-X^{12}-(CH_2)_n{}^{10}-$ in which: n^6 is 3, 4, 5 or 6 (preferably n^6 is 4 or 5), n^7 is 2, 3, 4, or 5 (preferably n^7 is 2, 3 or 4), n^8 and n^9 and n^{10}

independently are 2 or 3 (independently preferably 2) and X^{12} is O or NR^{14} wherein R^{14} is H or C_{1-2}alkyl;

R^{15} is a hydrogen atom (H); C_{1-4}alkyl (e.g. ^{t}Bu or C_{1-2}alkyl e.g. methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

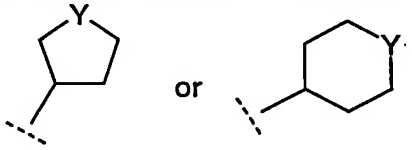
R^{16} is C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl; pyridinyl (e.g. pyridin-2-yl); or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; and

$R^{19}$is a hydrogen atom (H); C_{1-4}alkyl (e.g. isobutyl, sec-butyl, or C_{1-3}alkyl such as methyl or isopropyl); $-(CH_2)_{n^{20}}-OR^{20}$ wherein n^{20} is 1, 2, 3 or 4 (preferably 1) and R^{20} is a hydrogen atom (H) or C_{1-4}alkyl (preferably R^{20} is H); -CH(Me)-OH; $-CH_2$-SH; $-CH_2-CH_2$-S-Me; benzyl; or (4-hydroxyphenyl)methyl (i.e. 4-hydroxy-benzyl).

Preferably, where X is OR^{5a}, the compound is other than the compound wherein R^1 is methyl, X is OEt, and R^3 is cyclopentyl.

In one optional embodiment of the invention, R^1 is hydrogen, C_{1-4}alkyl, C_{1-2}fluoroalkyl, phenyl or benzyl.

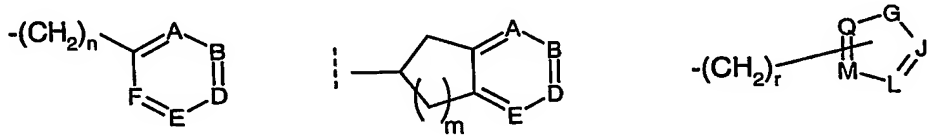
Alternatively or additionally, in one optional embodiment of the invention, R^2 is a hydrogen atom (H).

Alternatively or additionally, in one optional embodiment of the invention, R^3 is C_{3-8}cycloalkyl or a heterocyclic group being  in which Y is O, S, SO_2, or NR^{10}; where R^{10} is hydrogen, C_{1-4}alkyl, C_{1-2}fluoroalkyl, C(O)-C_{1-2}alkyl, or C(O)-CF_3;

and wherein in R^3 the C_{3-8}cycloalkyl or heterocyclic group is optionally substituted with one or two substituents being OH, C_{1-2}alkoxy, trimethoxy, or C_{1-2}alkyl; and wherein any OH, alkoxy or trimethoxy substituent is not substituted at the (R^3) ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either (R^3) ring carbon bonded to the Y group of the heterocyclic group.

Alternatively or additionally, in one optional embodiment of the invention, R^4 is hydrogen, C_{1-2}alkyl or C_{1-2}fluoroalkyl.

Alternatively or additionally, in one optional embodiment of the invention, R^5 is hydrogen, C_{1-8}alkyl, C_{1-8} fluoroalkyl, or C_{3-8}cycloalkyl; or phenyl optionally substituted with one or two of: a halogen atom, C_{1-2}alkyl, trifluoromethyl, C_{1-2}alkoxy or trifluoromethoxy; or R^5 has the sub-formula (x), (y) or (z):



(x) (y) (z)

wherein in sub-formula (x), n = 1 or 2; in sub-formula (y), m = 1 or 2; and in sub-formula (z), r = 1 or 2;

wherein in sub-formula (x) and (y), none, one or two of A, B, D, E and F are nitrogen; and the remaining of A, B, D, E and F are CH or CR^6 where R^6 is a halogen atom, C_{1-4}alkyl, C_{1-4}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy, C_{1-2}alkylsulphonyl (C_{1-2}alkyl-SO_2-), C_{1-2}alkyl-SO_2-NH-, R^7R^8N-SO_2-, R^7R^8N-CO-, R^7R^8N, OH, C_{1-4}alkoxymethyl, or C_{1-2}alkyl-SO_2-CH_2-, wherein R^7 and R^8 are independently hydrogen or C_{1-2}alkyl;

wherein in sub-formula (z), G is O or S or NR^9 wherein R^9 is C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one or two of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are CH or CR^6 where R^6 is as defined herein.

In the alternative to the above R^4 and/or R^5 optional embodiments, in one optional embodiment of the invention, R^4 and R^5 taken together can be $-(CH_2)_{p^1}-$ where $p^1 = 3$, 4 or 5 (preferably $p^1 = 4$ or 5).

In compounds, for example in the compounds of formula (I), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl or any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, or the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy or C_{1-2}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C_{3-8}cycloalkyl group is C_{3-6}cycloalkyl or C_{5-6}cycloalkyl , that is contains a 3-6 membered or 5-6 membered carbocyclic ring.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), 2-fluoroethyl (CH_2FCH_2-), etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), can be a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo").

When the specification states that atom or moiety A is "bonded" or "attached" to atom or moiety B, it means that atom/moiety A is directly bonded to atom/moiety B usually by means of one or more covalent bonds, and excludes A being indirectly attached to B via one or more intermediate atoms/moieties (e.g. excludes A-C-B); unless it is clear from the context that another meaning is intended.

Preferably, R^1 is a hydrogen atom (H), C_{1-4}alkyl, C_{1-3}fluoroalkyl, $-CH_2CH_2OH$ or $-CH_2CH_2CO_2Et$; more preferably C_{1-3}alkyl, C_{1-2}fluoroalkyl, or $-CH_2CH_2OH$; still more preferably C_{1-3}alkyl, C_2fluoroalkyl or $-CH_2CH_2OH$ such as methyl, ethyl, n-propyl or $-CH_2CH_2OH$; yet more preferably C_{2-3}alkyl, C_2fluoroalkyl or $-CH_2CH_2OH$ such as ethyl, n-propyl or $-CH_2CH_2OH$. R^1 is most preferably ethyl.

Preferably, R^2 is a hydrogen atom (H) or methyl, more preferably a hydrogen atom (H).

Preferably, in R^3 there is one substituent or no substituent.

In one optional embodiment, where R^3 is optionally substituted C_{3-8}cycloalkyl, it is not optionally substituted C_5cycloalkyl, i.e. not optionally substituted cyclopentyl. In this case, more preferably, R^3 is optionally substituted C_{6-8}cycloalkyl.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, it is more preferably C_6cycloalkyl (i.e. cyclohexyl) optionally substituted with one or two substituents being oxo (=O), OH, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy), or C_{1-2}alkyl, and wherein any OH, alkoxy or fluoroalkoxy substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I).

Where R^3 is optionally substituted C_{3-8}cycloalkyl, the one or two optional substituents preferably comprise (e.g. is or are) OH and/or oxo (=O).

Optionally, in R^3, the C_{3-8}cycloalkyl can be unsubstituted.

Where R^3 is optionally substituted C_{3-8}cycloalkyl, e.g. optionally substituted C_{5-8}cycloalkyl such as optionally substituted C_6cycloalkyl (optionally substituted cyclohexyl), the one or two optional substituents if present optionally comprise (e.g. is or are) a substituent at the 3-, 4- or 5- position of the R^3 cycloalkyl ring. Any OH substituent is more preferably at the 3- or 5-position of the R^3 cycloalkyl ring. (In this connection, the 1-position of the R^3 cycloalkyl ring is deemed to be the connection point to the -NH- in formula (I)).

Where R^3 is optionally substituted C_{3-8}cyclohexyl, R^3 is still more preferably cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), OH, C_{1-2}alkoxy or C_{1-2}fluoroalkoxy substituent; more preferably R^3 is cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O) or OH substituent. The optional substituent is preferably at the 3- or 4- position of the R^3 cyclohexyl ring; more preferably any OH substituent is preferably at the 3-position of the R^3 cyclohexyl ring.

Where R^3 is optionally substituted C_6cycloalkyl, R^3 can for example be 4-hydroxy-cyclohexyl (i.e. 4-hydroxycyclohexan-1-yl), but R^3 is more preferably cyclohexyl (i.e. unsubstituted) or 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) or 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl).

Where R^3 is optionally substituted C_5cycloalkyl (optionally substituted cyclopentyl), R^3 can for example be cyclopentyl (i.e. unsubstituted) or 3-hydroxy-cyclopentyl.

Where R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then Y is preferably O, S, SO_2, NH or N-C(O)methyl, more preferably O, NH or N-C(O)methyl, still more preferably O or N-C(O)methyl, most preferably O. (When Y is NH or N-C(O)methyl, then R^{10} is H or C(O)methyl).

Preferably, R^{10} is a hydrogen atom (H), methyl, ethyl, $C(O)NH_2$, C(O)methyl or $C(O)\text{-}CF_3$. Optionally, R^{10} can be a hydrogen atom (H), methyl, ethyl, C(O)methyl or $C(O)\text{-}CF_3$, more preferably H, C(O)methyl or $C(O)\text{-}CF_3$, still more preferably H or C(O)methyl.

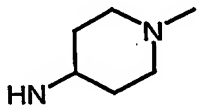
Where R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then it is preferable that R^3 is the heterocyclic group of sub-formula (aa) or (bb), more preferably of sub-formula (bb).

In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.

Suitably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) is unsubstituted (In this connection, where Y is NR^{10}, R^{10} is not classified as a substituent).

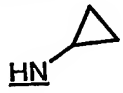
In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents preferably comprise (e.g. is or are) OH and/or oxo.

When R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then preferably R^{10} is not C(O)-Me. More preferably, when R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is preferably not C(O)R, i.e. or e.g. R^{10} is preferably not $C(O)NH_2$, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl. In one embodiment, Y is O, S, SO_2 or NH when R^3 is the heterocyclic group of sub-formula (aa).

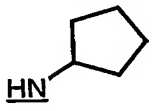
Optionally, according to one embodiment of the invention, NHR^3 is not 

. More preferably, when R^3 is the heterocyclic group of sub-formula (bb) and Y is NR^{10}, and optionally when n^1 is 1, then preferably R^{10} is not methyl. More preferably, when R^3 is the heterocyclic group of sub-formula (bb) and Y is NR^{10}, and optionally when n^1 is 1, then R^{10} is preferably not alkyl or substituted alkyl, i.e. or e.g. R^{10} is preferably not C_{1-4}alkyl (e.g. methyl or ethyl), C_{1-2}fluoroalkyl or $CH_2C(O)NH_2$. In one embodiment, when R^3 is the heterocyclic group of sub-formula (bb), Y is preferably O, S, SO_2 or NR^{10}, wherein R^{10} is H, $C(O)NH_2$, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl, or more preferably Y ias H or C(O)Me. More preferably, for sub-formula (bb), Y is O or NR^{10}.

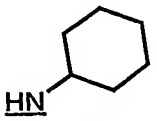
Preferably, NHR^3 is of sub-formula (a), (b), (c), (d), (e), (f), (g), (g1), (g2), (g3), (h), (i), (j), (k), (L), (m), (n), (o), (p), or (q):



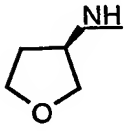
(a)



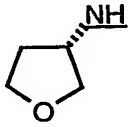
(b)



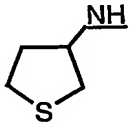
(c)



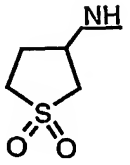
(d)



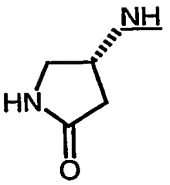
(e)



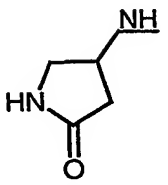
(f)



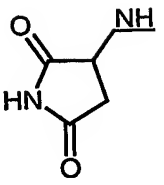
(g)



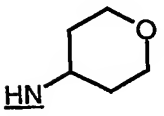
(g1)



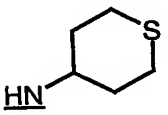
(g2)



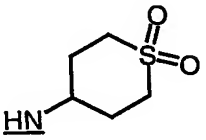
(g3)



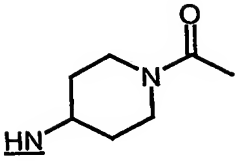
(h)



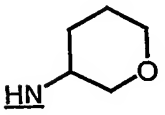
(i)



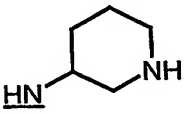
(j)



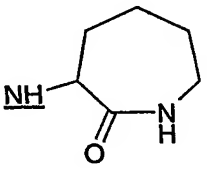
(k)



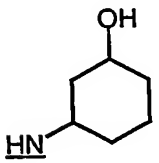
(L)



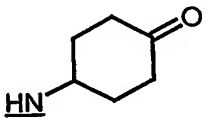
(m)



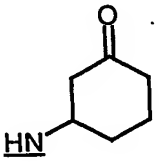
(m1)



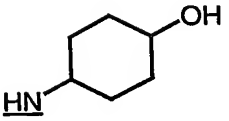
(n)



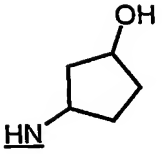
(o)



(o1)



(p)



(q)

In the sub-formulae (a) to (q) etc above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

Preferably, NHR^3 is of sub-formula (c), (d), (e), (f), (g1), (h), (i), (j), (k), (m), (m1), (n), (o), (o1), (p), or (q). More preferably NHR^3 is of sub-formula (c), (h), (k), (n), or (o). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl; that is NHR^3 is most preferably of sub-formula (h), as shown above.

Preferably, X is NR^4R^5.

Where R^4 is C_{1-6}alkyl, then preferably it is C_{1-4}alkyl or C_{1-2}alkyl. Where R^4 is C_{1-3}fluoroalkyl then preferably it is C_{1-2}fluoroalkyl.

Most preferably, R^4 is a hydrogen atom (H).

Where R^4 is C_{2-6}alkyl substituted by one substituent R^{11}, then preferably R^4 is C_{2-4}alkyl (e.g. C_{2-3}alkyl) substituted by one substituent R^{11}. More preferably, R^4 is $-(CH_2)_{n^3}-R^{11}$ wherein n^3 is 2, 3 or 4. Still more preferably, n^3 is 2 and/or R^4 is $-(CH_2)_{n^3}-OH$.

When R^5 is C_{2-6}alkyl substituted by one or two independent substituents R^{11}, it is preferable that R^5 is C_{2-4}alkyl (e.g. C_{2-3}alkyl) substituted by one or two independent substituents R^{11}. When R^5 is C_{2-6}alkyl (e.g. C_{2-4}alkyl or C_{2-3}alkyl) substituted by one or two independent substituents R^{11}, it is preferable that R^5 is C_{2-6}alkyl (e.g. C_{2-4}alkyl or C_{2-3}alkyl) substituted by one substituent R^{11}. It is more preferable that R^5 is $-(CH_2)_{n^5}-R^{11}$ wherein n^5 is 2, 3 or 4. Preferably n^5 is 2 or 3, more preferably 2.

Preferably, each substituent R^{11}, independently of any other R^{11} substituent present, is: hydroxy (OH); C_{1-6}alkoxy (e.g. C_{1-4}alkoxy such as t-butyloxy, ethoxy or methoxy); phenyloxy; benzyloxy; $-NR^{12}R^{13}$; $-NR^{15}-C(O)R^{16}$; $-NR^{15}-C(O)-NH-R^{15}$; or $-NR^{15}-SO_2R^{16}$ (more preferably C_{1-6}alkoxy, $-NR^{15}-C(O)-NH-R^{15}$, or $-NR^{15}-SO_2R^{16}$; most preferably $-NR^{15}-SO_2R^{16}$). In all cases, any R^{11} substituent which is OH, alkoxy or $-NR^{12}R^{13}$ is not substituted at any carbon atom, of any R^4 or R^5 substituted alkyl, which is bonded to the nitrogen of NR^4R^5.

Where R^5 is C_{1-8}alkyl, then preferably it is C_{1-5}alkyl or C_{1-3}alkyl. Where R^5 is C_{1-8}fluoroalkyl then preferably it is C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl. Where R^5 is C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group, then preferably the C_{3-8}cycloalkyl is not substituted at the ring-carbon bonded to the nitrogen of NR^4R^5. Where R^5 is optionally substituted C_{3-8}cycloalkyl, then more preferably it is C_{3-8}cycloalkyl (i.e. unsubstituted).

When R^5 is optionally substituted $-(CH_2)_{n^4}-C_{3-8}$cycloalkyl wherein n^4 is 1, 2 or 3, then n^4 is preferably 1 or 2 or more preferably 1, and/or preferably R^5 is optionally substituted

-$(CH_2)_n^4$-C_{5-6}cycloalkyl or optionally substituted -$(CH_2)_n^4$-C_6cycloalkyl. When R^5 is optionally substituted -$(CH_2)_n^4$-C_{3-8}cycloalkyl, preferably it is not substituted. Most preferably R^5 is (cyclohexyl)methyl-, that is -CH_2-cyclohexyl.

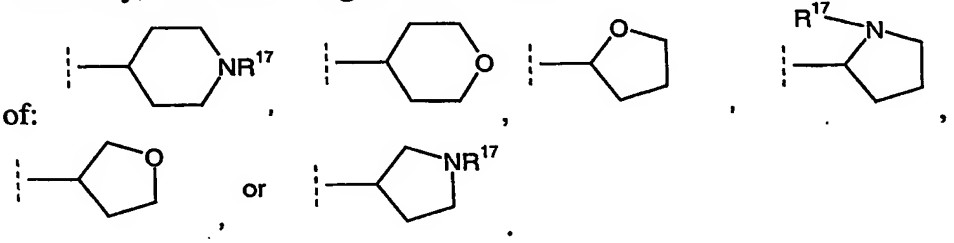
When R^5 is -$(CH_2)_n^{11}$-C(O)R^{16}; -$(CH_2)_n^{11}$-C(O)$NR^{12}R^{13}$; -CHR^{19}-C(O)$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-C(O)OR^{16}; -CHR^{19}-C(O)OR^{16}; -$(CH_2)_n^{12}$-SO_2-$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-SO_2R^{16}; or -$(CH_2)_n^{12}$-CN; then in one embodiment of the invention R^5 can be: -$(CH_2)_n^{11}$-C(O)R^{16}; -$(CH_2)_n^{11}$-C(O)$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-C(O)OR^{16}; -$(CH_2)_n^{12}$-SO_2-$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-SO_2R^{16}; or -$(CH_2)_n^{12}$-CN.

When R^5 is -$(CH_2)_n^{11}$-C(O)R^{16}; -$(CH_2)_n^{11}$-C(O)$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-C(O)OR^{16}; -$(CH_2)_n^{12}$-SO_2-$NR^{12}R^{13}$; -$(CH_2)_n^{12}$-SO_2R^{16}; or -$(CH_2)_n^{12}$-CN; then R^5 can for example be -$(CH_2)_n^{11}$-C(O)R^{16}; -$(CH_2)_n^{11}$-C(O)$NR^{12}R^{13}$; or -$(CH_2)_n^{12}$-CN; preferably -$(CH_2)_n^{11}$-C(O)R^{16}.

Preferably, n^{11} is 1 or 2. Advantageously, n^{12} is 1 or 2.

When R^5 is -$(CH_2)_n^{13}$-Het, it is preferable that n^{13} is 0, 1 or 2, more preferably 0 or 1.

Preferably, Het is a 5- or 6-membered saturated or partly-saturated heterocyclic ring and/or preferably is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring. Preferably, the heterocyclic ring Het contains one ring-hetero-atom selected from O, S and N. Preferably, the carbon ring-atoms in Het are not substituted. Het is most preferably one of:



When R^5 is optionally substituted phenyl, then preferably R^5 is phenyl optionally substituted with one or two (preferably one) of: a halogen atom (preferably fluoro and/or chloro); C_{1-2}alkyl; C_{1-2}fluoroalkyl (e.g. trifluoromethyl); C_{1-2}alkoxy (e.g. methoxy); trifluoromethoxy; C_{1-2}alkylsulphonyl (C_{1-2}alkyl-SO_2-); C_{1-2}alkyl-SO_2-NH-; R^7R^8N-SO_2-; R^7R^8N-CO-; -NR^{15}-C(O)R^{16}; R^7R^8N; OH; C_{1-2}alkoxymethyl; C_{1-2}alkyl-SO_2-CH_2-; cyano (CN); or phenyl optionally substituted by one of fluoro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy. More preferably R^5 is phenyl optionally substituted with one or two (preferably one) of: a halogen atom, C_{1-2}alkyl,

trifluoromethyl, C_{1-2}alkoxy, trifluoromethoxy, R^7R^8N-SO_2-, R^7R^8N-CO-, or C_{1-2}alkyl-SO_2-CH_2-. When R^5 is optionally substituted phenyl, then preferably one or all of the one or two optional substituents are substituted at the *meta*- (3- and/or 5-) and/or *para*- (4-) position(s) of the phenyl ring with respect to the phenyl ring-carbon bonded to the nitrogen of NR^4R^5.

Preferably, R^7 and/or R^8 are independently a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_{3-6}cycloalkyl; or phenyl optionally substituted by one of: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or R^7 and R^8 together are $-(CH_2)_n{}^6-$ or $-(CH_2)_n{}^8-X^7-(CH_2)_n{}^9-$ wherein X^7 is NR^{14} or preferably O.

When R^7 is cycloalkyl or optionally substituted phenyl, then preferably R^8 is neither cycloalkyl nor optionally substituted phenyl.

Most preferably, R^7 and/or R^8 independently are a hydrogen atom (H) or C_{1-2}alkyl. It is preferable that R^7 is a hydrogen atom (H).

Preferably n^6 is 4 or 5. Preferably n^7 is 2, 3 or 4. Preferably, n^8, n^9 and/or n^{10} is/are independently 2.

In general, it is preferable that R^5 has the sub-formula (x) or (y) or (z).

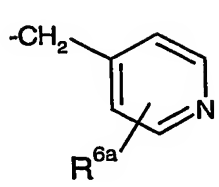
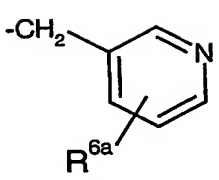
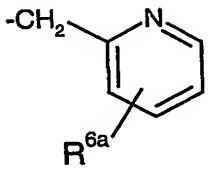
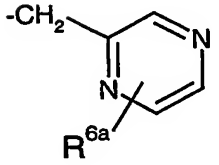
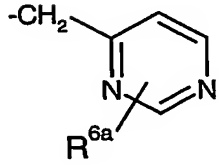
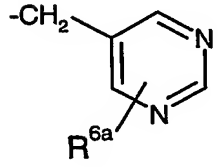
When R^5 has the sub-formula (x) or (y) or (z), preferably R^5 has the sub-formula (x) or (y), more preferably (x).

Preferably n = 1. Preferably, m = 1. Preferably, r = 1 or 2, more preferably 1.

In sub-formula (x) and/or (y), it is preferred that none, one or two of A, B, D, E and F are nitrogen; none, one, two or three of A, B, D, E and F are CR^6; and the remaining of A, B, D, E and F are CH. More preferably, none, one or two of A, B, D, E and F are nitrogen; none or one of A, B, D, E and F are CR^6; and the remaining of A, B, D, E and F are CH.

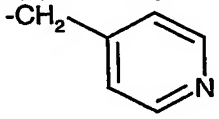
In sub-formula (x) and/or (y), preferably, none or one of A, B, D, E and F are nitrogen, and/or preferably none of A, B, D, E and F are CR^6.

Preferably, sub-formula (x) is: benzyl; phenethyl (Ph-C_2H_4-); benzyl substituted on the phenyl ring with a single R^6 substituent; phenethyl (Ph-C_2H_4-) substituted on the phenyl ring with a single R^6 substituent; or one of the following:

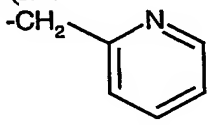







, wherein R^{6a} is either R^6 as defined herein or (preferably) hydrogen.

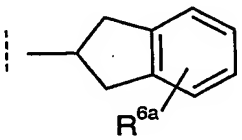
Most preferably, sub-formula (x) is benzyl or pyridinylmethyl



[e.g. pyridin-4-ylmethyl (i.e.), pyridin-3-ylmethyl, or preferably



pyridin-2-ylmethyl (i.e.)].



Preferably, sub-formula (y) is: , wherein R^{6a} is either R^6 as defined herein or preferably hydrogen.

Preferably, in sub-formula (z), none, one or two of J, L, M and Q are nitrogen.

In sub-formula (x), (y) and/or (z), preferably, R^6 is a fluorine or chlorine atom, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, methyl-SO_2-NH-, Me_2N-SO_2-, -$CONH_2$, -CONHMe, NMe_2, t-butoxymethyl, or methyl-SO_2-CH_2-. More preferably, R^6 is a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy, methyl-SO_2-NH-, Me_2N-SO_2- or -$CONH_2$.

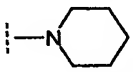
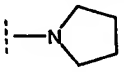
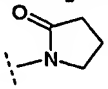
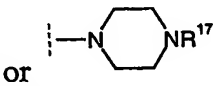
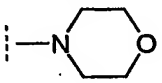
In sub-formula (x) and/or (y), optionally, one, two or three R^6 substituents are present in B, D and/or E, so that in sub-formula (x) one, two or three R^6 substituents are present in the meta- (3- and/or 5-) and/or para- (4-) positions with respect to the $-(CH_2)_n-$ side-chain.

In sub-formula (x) and/or (y), preferably, any optional R^6 substituent is present only in B, D and/or E, so that in sub-formula (x) any optional R^6 substituent is present only in the meta- (3- and/or 5-) and/or para- (4-) positions with respect to the $-(CH_2)_n-$ side-chain. Alternatively, in sub-formula (x), any optional R^6 substituent can be present in the ortho- (2- and/or 6-) position with respect to the $-(CH_2)_n-$ side-chain, either alone or in combination with one or more other optional R^6 substituents.

Overall for R^5, it is preferable that R^5 is a hydrogen atom (H), C_{1-6}alkyl (e.g. C_{3-6}alkyl), C_{1-4}fluoroalkyl, C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl), phenyl optionally substituted with one of: a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy or trifluoromethoxy; or R^5 has the sub-formula (x), (y) or (z), for example as described above; or R^4 and R^5 taken together are $-(CH_2)_p-$ where p = 4 or 5.

Still more preferably, R^5 is a hydrogen atom (H), methyl, ethyl, n-propyl, iso-propyl, 2-ethylbutan-1-yl, cyclopentyl, cyclohexyl, fluorophenyl e.g. 4-fluorophenyl, benzyl, or pyridinylmethyl; or R^4 and R^5 taken together are $-(CH_2)_p-$ where p = 4. Most preferably, R^5 is benzyl, pyridinylmethyl (e.g. pyridin-4-ylmethyl, pyridin-3-ylmethyl, or preferably pyridin-2-ylmethyl), or 4-fluorophenyl.

When R^4 and R^5 taken together are optionally substituted $-(CH_2)_p{}^1-$ or optionally substituted $-C(O)-(CH_2)_p{}^2-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ or $-C(O)-X^5-(CH_2)_p{}^5-$ or a partially unsaturated derivative of any of the foregoing, preferably R^4 and R^5 taken together are optionally substituted $-(CH_2)_p{}^1-$ or optionally substituted $-C(O)-(CH_2)_p{}^2-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ or $-C(O)-X^5-(CH_2)_p{}^5-$ (i.e. not a partially unsaturated derivative of any of these).

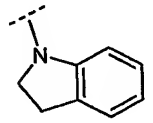
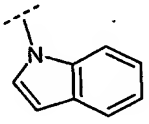
When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ optionally substituted by R^{18}, or $-C(O)-(CH_2)_p{}^2-$ optionally substituted by R^{18}, or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$, NR^4R^5 can for example be  optionally substituted by R^{18}, or  optionally substituted by R^{18}, or  optionally substituted by R^{18}, or  (i.e. R^4 and R^5 taken together are $-(CH_2)_2-N(R^{17})-(CH_2)_2-$), or  (i.e. R^4 and R^5 taken together are $-(CH_2)_2-O-(CH_2)_2-$).

Preferably, R^{17} is a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl; $-(CH_2)_p{}^6-C(O)R^{16}$, or the optionally substituted phenyl or benzyl. More preferably, R^{17} is H; C_{1-2}alkyl; $-(CH_2)_p{}^6-C(O)R^{16}$ or the optionally substituted phenyl.

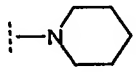
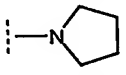
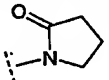
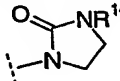
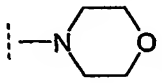
When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$, the NR^4R^5 heterocycle is preferably not substituted by R^{18}.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$, and if the NR^4R^5 heterocycle is substituted by R^{18}, then optionally R^{18} is not substituted at a ring-carbon bonded to the NR^4R^5 ring-nitrogen.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-C(O)-(CH_2)_p{}^2-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ or $-C(O)-X^5-(CH_2)_p{}^5-$ or a partially unsaturated derivative of any of these, and wherein the NR^4R^5 heterocycle is fused to a phenyl ring optionally substituted on the phenyl by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; then in one embodiment of the invention NR^4R^5 is

 or 

wherein the phenyl is optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy.

In one embodiment of the invention, NR^7R^8 and/or $NR^{12}R^{13}$ can for example independently be  or  or  or  , or  (i.e. R^{12} and R^{13} together or R^7 and R^8 together are $-(CH_2)_2-N(R^{14})-(CH_2)_2-$), or  (i.e. R^{12} and R^{13} together or R^7 and R^8 together are $-(CH_2)_2-O-(CH_2)_2-$).

Preferably, R^{15} is a hydrogen atom (H) or C_{1-4}alkyl (e.g. ^{t}Bu or C_{1-2}alkyl e.g. methyl); more preferably, R^{15} is a hydrogen atom (H).

Preferably, however, R^4 and R^5 are not taken together , i.e. are not taken together to form the NR^4R^5 ring systems described herein.

(Similar preferances apply for R^{5a} as for R^5, except that R^{5a} cannot be a hydrogen atom. Most preferably, R^{5a} is ethyl.)

In an especially preferable embodiment, NR^4R^5 is the NR^4R^5 group as defined in any one of: Examples 21-98, 100-182, 184, 187-188, and 191-200.
It is particularly preferred that the compound of formula (I) or the salt thereof is:

Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,
N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine,
1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine,

4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-n-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, **or**
4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of these specific compounds are given in Examples 1-98 hereinafter.

Alternatively, it is particularly preferred that the compound of formula (I) or the salt thereof is:

1-Ethyl-*N*-[4-(methylsulfonyl)benzyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
tert-Butyl (1-{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperidin-3-yl)methylcarbamate,
1-Ethyl-*N*-[3-(methylsulfonyl)benzyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-5-{[5-methoxy-6-(trifluoromethyl)-2,3-dihydro-1*H*-indol-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
N-[(5-Chloropyridin-2-yl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,

N-(4-Chlorobenzyl)-1-ethyl-*N*-isopropyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(3-Chlorobenzyl)-1-ethyl-*N*-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(5-methyl-3-phenylisoxazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(2-*tert*-Butoxyethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(1,3-thiazol-2-ylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(pyrimidin-4-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(2-methyl-1,3-thiazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[3-(*tert*-Butoxymethyl)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{2-[methyl(methylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(pyrazin-2-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-5-{[4-(pyridin-2-ylcarbonyl)piperazin-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
N-(2-Chloro-6-fluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(6-oxo-1,6-dihydropyridin-3-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[3-(Aminocarbonyl)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{4-[(methylamino)carbonyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-{2-[(Anilinocarbonyl)amino]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(1*H*-tetraazol-5-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[2-(1*H*-1,2,4-triazol-1-yl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
tert-Butyl 2-[{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}(methyl)amino]ethylcarbamate,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[4-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,

tert-Butyl 4-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)piperidine-1-carboxylate,
1-Ethyl-*N*-{3-[(methylsulfonyl)amino]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[2-(Dimethylamino)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(tetrahydrofuran-2-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-ethyl-*N*-tetrahydro-2*H*-pyran-4-yl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-{4-[(Dimethylamino)sulfonyl]benzyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{3-[(methylsulfonyl)amino]benzyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperidine-2-carboxamide,
1-Ethyl-*N*-(4-methoxyphenyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(pyridin-3-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(1-methylpiperidin-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(1-ethylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(2-piperidin-1-ylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(3-morpholin-4-ylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(3-Ethoxypropyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(Cyclohexylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[3-(Dimethylamino)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-neopentyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,

1-ethyl-*N*-(4-methoxybenzyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{2-[(phenylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[2-(Acetylamino)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{2-[(methylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-methyl-*N*-(pyridin-4-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{2-[(2-methoxyphenyl)(methyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-(2-oxo-2-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1H-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(2,5-Difluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N,1-Diethyl-*N*-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(2-amino-2-oxoethyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-*N*-(3-methoxyphenyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(3,4-Difluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
Ethyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)propanoate,
N-(1-Benzylpiperidin-4-yl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Butyl-4-{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperazine-1-carboxamide,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(1,3,4-thiadiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(2,3-Dihydro-1*H*-inden-2-yl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(3,4-Dimethoxybenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,

N-(3-Chlorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-5-[(4-methylpiperazin-1-yl)carbonyl]-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-*N*-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-5-{[4-(4-methoxyphenyl)piperazin-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine,
1-Ethyl-*N*-{4-[(methylsulfonyl)methyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[3-(dimethylamino)-3-oxopropyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,
1-Ethyl-*N*-[(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-{4-[(methylamino)sulfonyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-(2-Cyanoethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-methyl-*N*-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-methyl-*N*-[(1-methyl-1*H*-imidazol-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2-thien-2-ylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-[2-(4-Chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[2-(2-methoxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
Ethyl 4-(cyclohexylamino)-1-(3-ethoxy-3-oxopropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate,
N-Benzyl-4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate,
Ethyl 1-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate,
N-[4-(Methylsulfonyl)benzyl]-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-b]pyridine-5-carboxamide,
N-(4-Fluorophenyl)-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate,

Ethyl 4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate,
4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-*N*-(4-fluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
4-(Cyclohexylamino)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(2-oxoazepan-3-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(3-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
N-Benzyl-1-ethyl-4-[(3-hydroxycyclopentyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide, **or**
N-Benzyl-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of these specific compounds are given in Examples 100-201 hereinafter.

Alternatively, the compound of formula (I) or the salt thereof can be:

1-Ethyl-*N*-(2-hydroxy-1-methylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide, or
Methyl (2*S*)-2-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-hydroxypropanoate;

or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. (See for example Examples 202-203).

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts. A pharmaceutically acceptable acid addition salt can

be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, fumarate, citrate, tartrate, benzoate, p-toluenesulfonate, methanesulfonate or naphthalenesulfonate salt. A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base, optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

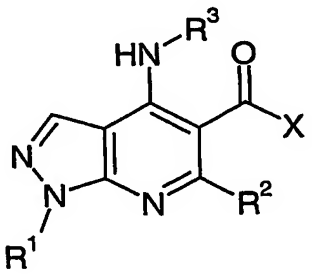
Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less, in particular 650 or less or 600 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

Synthetic Process Routes

The following processes can be used to make the compounds of the invention:

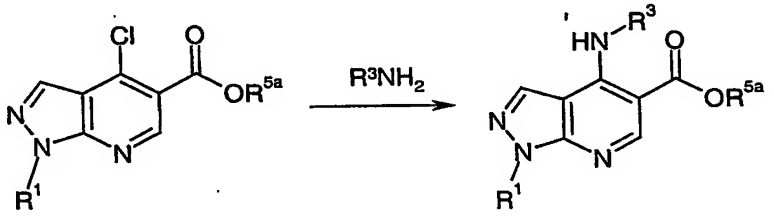


(I)

Most of the following synthetic processes following are exemplified for compounds of Formula (I) wherein R^2 is a hydrogen atom (H). However, some or all of these processes can also be used with appropriate modification, e.g. of starting materials and reagents, for making compounds of Formula (I) wherein R^2 is other than H.

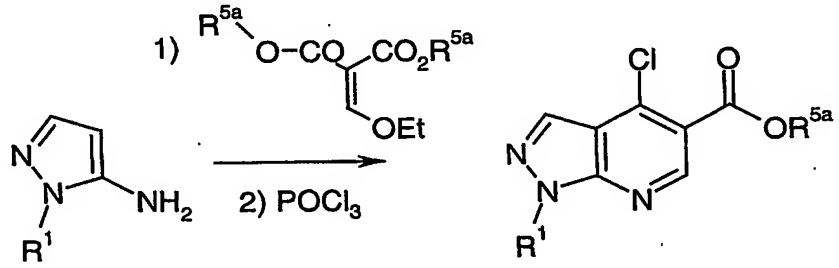
Process A

Compounds of formula (I) where X = OR^{5a}, can be prepared according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (II) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100 °C , for example ca. 80-90 °C:



(II) (I)

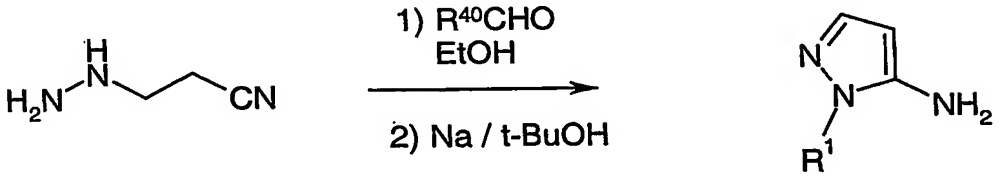
Compounds of formula (II) are also described in the above reference and can be prepared by reaction of a compound of formula (III) with, for example, diethylethoxymethylene malonate (where R^{5a} = Et) with heating, followed by reaction with phosphorous oxychloride, again with heating:



Formula III Formula II

Where the desired amino pyrazole of formula (III) is not commercially available (for example R^1 = CH_2Ph), preparation can be achieved using methods described by Dorgan et. al. in J. Chem. Soc., Perkin Trans. 1, (4), 938-42; 1980, by reaction of cyanoethylhydrazine with a suitable aldehyde of formula $R^{40}CHO$ in a solvent such as ethanol, with heating, followed by reduction with, for example sodium in a solvent such

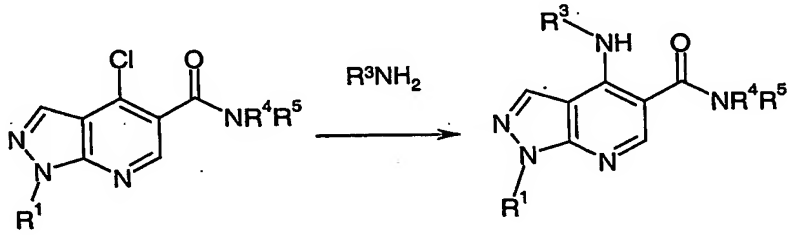
as t-butanol. R^{40} should be chosen so as to contain one less carbon atom than R^1, for example R^{40} = methyl will afford R^1 = ethyl.



Formula III

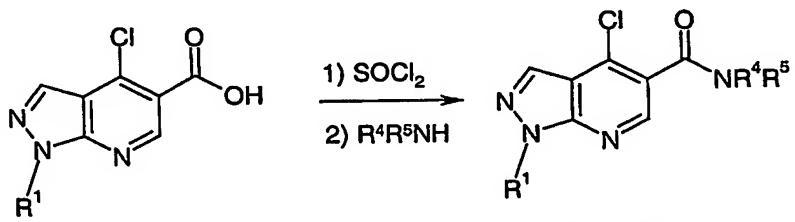
Process B

Compounds of formula (I) where X = NR^4R^5, can be prepared by reaction of a compound of formula (IV) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



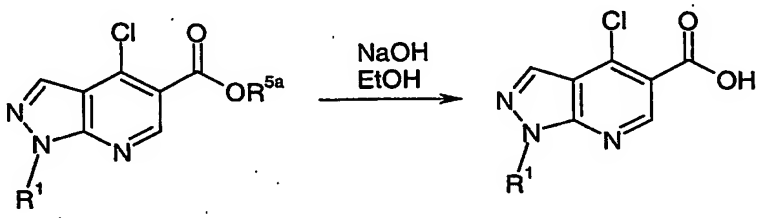
Formula IV Formula I

Compounds of formula (IV) can be prepared in a two step procedure as described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573. This process involves, first, reaction of a compound of formula (V) with thionyl chloride (or another agent suitable for forming an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed intermediate may or may not be isolated. Step two involves reaction with an amine of formula R^4R^5NH, in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethyl amine:



Formula V Formula IV

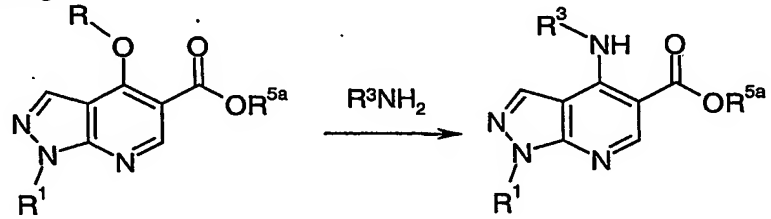
Compounds of formula (V) can be prepared by hydrolysis of an ester of formula (II) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane:



Formula II Formula V

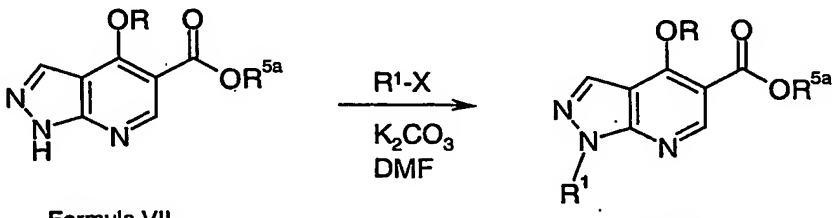
Process C

Compounds of formula (I) can also be prepared according to the method described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573, which involves reaction of a compound of formula (VI), in which -O-R is -O-C_{1-4}alkyl, in particular -O-Et, with an amine of formula R^3NH_2. The reaction may be carried out with or without solvent and may require heating.



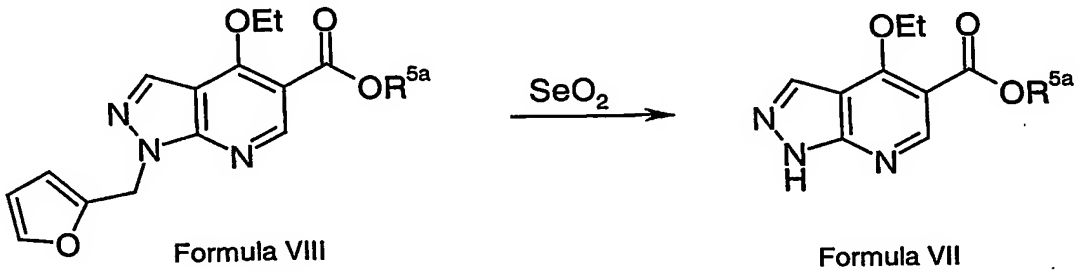
Formula VI Formula I

Compounds of formula (VI) (also described in the above reference) can be prepared by reaction of a compound of formula (VII) with a suitable alkylating agent of formula R^1-X, where X is a leaving group such as halogen. The reaction should be carried out in the presence of a base such as potassium carbonate, in an anhydrous solvent such as DMF:



Formula VII Formula VI

The preparation of compounds of formula VII by oxidative cleavage of compounds of formula VIII is described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573 (further referred to Zuleski et. al. in J. Drug. Metab. Dispos., 1985, 13,139).



Formula VIII Formula VII

Process D:

To form a compound of formula (I) wherein X = NR^4R^5, a compound of formula (I) but wherein X = OH (a carboxylic acid) can be converted into an activated compound of formula (I) but wherein X = a leaving group substitutable by an amine; and subsequently the activated compound can be reacted with an amine of formula R^4R^5NH. For example, the activated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein X = Cl. This can be formed from the carboxylic acid (X = OH) e.g. by thionyl chloride. See for example Examples 81-85.

The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof, comprising :

(a) for a compound of formula (I) wherein X = OR^{5a}, reaction of a compound of formula (II) with an amine of formula R^3NH_2, or

(b) for a compound of formula (I) wherein X = NR^4R^5, reaction of a compound of formula (IV) with an amine of formula R^3NH_2, or

(c) reaction of a compound of formula (VI), in which -O-R is -O-C_{1-4}alkyl, with an amine of formula R^3NH_2;

(d) to form a compound of formula (I) wherein X = NR^4R^5, conversion of a compound of formula (I) but wherein X = OH (a carboxylic acid) into an activated compound of formula (I) but wherein X = a leaving group substitutable by an amine (preferably, the activated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein X = Cl), and subsequent reaction of the activated compound with an amine of formula R^4R^5NH;

and optionally converting the compound of formula (I) into a salt e.g. a pharmaceutically acceptable salt.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein (e.g. for use in the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal) and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, or multiple sclerosis.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein) and COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein). COPD

is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (SL Wolda, 2000).

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly , the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral

pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose, e.g. of the dry powder composition, can be administered by inhalation via the device such as the DISKUS ^{TM} device, marketed by GlaxoSmithKline. The DISKUS ^{TM} inhalation device is usually substantially as described in GB 2,242,134 A. In such device at least one container for the pharmaceutical composition in powder form (the at least one container preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through which a user can inhale the pharmaceutical composition in powder form from the opened container.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.01 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Combinations

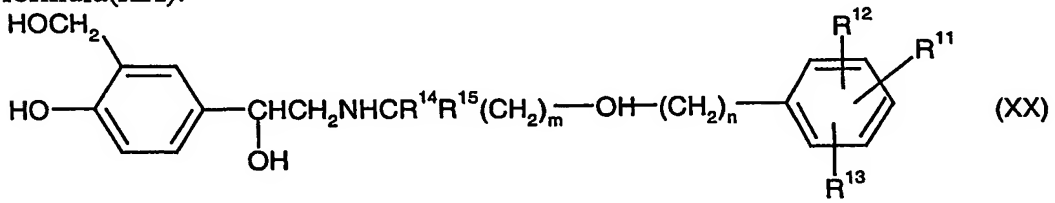
The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Examples of β_2-adrenoreceptor agonists include salmeterol (eg as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/66422A.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(XX):



(XX)

or a salt or solvate thereof, wherein in formula (XX):
m is an integer of from 2 to 8;
n is an integer of from 3 to 11,
with the proviso that m + n is 5 to 19,
R^{11} is $-XSO_2NR^{16}R^{17}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

R^{16} and R^{17} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18}R^{19}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{16} and R^{17}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16} and R^{17} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18}$, $-SO_2NR^{18}R^{19}$, $-CONR^{18}R^{19}$, $-NR^{18}C(O)R^{19}$, or a 5-, 6- or 7-membered heterocylic ring;
R^{18} and R^{19} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p is an integer of from 0 to 6, preferably from 0 to 4;
R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{14} and R^{15} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14} and R^{15} is not more than 4.

Examples of anti-histamines include methapyrilene or loratadine.

The invention also provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic compound, e.g. a muscarinic (M) receptor antagonist in particular an M_1, M_2, M_1/M_2, or M_3 receptor antagonist. For combinations of anticholinergic compounds / muscarinic (M) receptor antagonist with PDE4 inhibitors, see for example WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1, and some or all of these publications give examples of anticholinergic compounds / muscarinic (M) receptor antagonists which may be used with the compounds of formula (I) or salts.

Other suitable combinations include, for example, other anti-inflammatory agents eg. NSAIDs (eg. leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or antiinfective agents (eg. antibiotics, antivirals).

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition.

Biological Test Methods

PDE 3, PDE 4B, PDE 5 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5.

Human recombinant PDE4B

Human recombinant PDE4B, in particular one splice variant thereof, is disclosed in WO 94/20079 and also M.M. McLaughlin et al. (A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA, *J. Biol. Chem.*, 1993, **268**, 6470-6476). Human recombinant PDE4B was expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62. 100,000 x *g* supernatant fractions of yeast cell lysates were used for PDE4B assays and inhibitor studies.

Inhibition of PDE 3, PDE 4B, or PDE 5 activity

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant), PDE3 (from bovine aorta) or PDE5 (human recombinant) was determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so that no more than 20% hydrolysis of the substrate occurred in control wells without compound, during the incubation. For PDE3 and PDE4B assay [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.559) was added to give 0.05uCi per well and ~ 10nM final concentration. For PDE5 assay [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech , code TRK.392) was added to give 0.05uCi per well and ~ 36nM final concentration. Plates were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for , 1hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited) Results were expressed as pIC_{50} values.

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an avarage of ca. 2-6 readings) are as follows. Absolute accuracy is not possible, and the readings given are accurate only up to about ± 0.5 of a log unit:

Example	PDE4B pIC_{50}
2	8.0
3	7.8
11	7.4
21	8.5
22	7.9
32	7.7
40	8.3
63	6.9
196	7.9
198	8.5

Most or substantially all of the Examples have PDE4B inhibitory activities in the range of pIC_{50} = about 5 (± 0.5) to about 8.8 (± 0.5), more usually about 6 (± 0.5) to about 8.8 (± 0.5).

Emesis: Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention were to cause only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting, retching and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

Other side effects: Many known PDE4 inhibitors cause other side effects such as headache and other central nervous sytem (CNS-) mediated side effects; and/or gastrointestinal (GI) tract disturbances. Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound of the invention were to cause only limited or manageable side-effects in one or more of these side-effect categories.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were

specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

Abbreviations used herein:

DCM	dichloromethane
EtOAc	ethyl acetate
Et_2O	diethyl ether
DMF	dimethyl formamide
MeOH	methanol
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, H = no. of protons)
LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	hydroxybenzotriazole
h	hours
DIPEA	diisopropylethyl amine ($^iPr_2NEt$)
T_{RET}	retention time
THF	Tetrahydrofuran
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide

Machine Methods used herein:

LCMS (liquid chromatography/mass spectroscopy)
Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS
Flow Rate : 3ml/min

Injection Volume : 5µl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Intermediates and Examples

All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

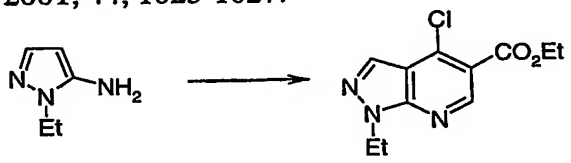
Table of Intermediates

Inter-mediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
4	Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
6	1-Acetyl-4-aminopiperidine
7	1-Methyl-4-aminopiperidine
8	4-Aminotetrahydropyran
8A	Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride
9	(R)-(+)-3-Amino tetrahydrofuran 4-toluene sulphonate
10	(S)-(-)-3-Amino tetrahydrofuran 4-toluene sulphonate
11	Tetrahydro-2H-thiopyran-4-amine
12	Tetrahydro-3-thiopheneamine
13	Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride
14	Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride
15	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

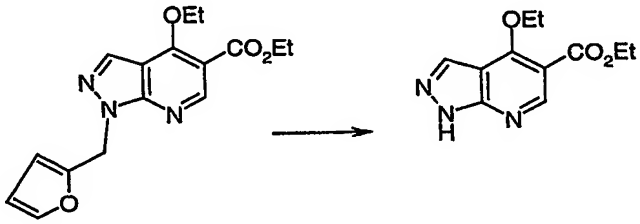
16	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
17	N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
18	4-Chloro-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
19	4-Chloro-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
20	4-Chloro-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
21	4-Chloro-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridine
22	4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
23	4-Chloro-1-ethyl-N-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
24	4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
25	Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
26	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
27	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
28	N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
29	4-Chloro-1-methyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
30	4-Chloro-1-methyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
31	4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
32	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
33	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
34	Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
35	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
36	Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
37	Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
38	Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
39	Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
40	Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
41	1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
42	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
43	1-Ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
44	1-Ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic

	acid
45	4-(Cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
46	4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
47	4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
48	Ethyl 4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
49	4-(Cyclohexylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
50	1-n-Propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
51	Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
52	4-(Cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
53	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
54	4-Aminocyclohexanone hydrochloride

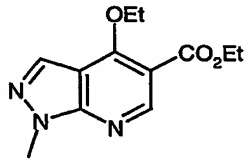
Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:



Intermediate 2: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
Can be prepared by oxidative cleavage (SeO_2) of 1-furanylmethyl derivative, as described by T. M. Bare *et. al.* In *J. Med. Chem.*, 1989, 32, 2561-2573, (further referenced to Zuleski, F. R., Kirkland, K. R., Melgar, M. D.; Malbica, *J. Drug. Metab. Dispos.*, 1985, 13, 139)

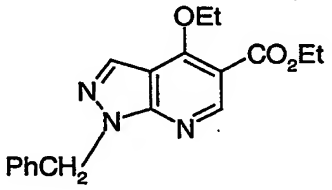


Intermediate 3: Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



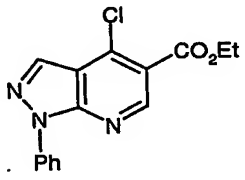
A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous dimethylformamide (DMF) (4ml) was treated with iodomethane (0.26ml) and stirred vigorously for 3h. The mixture was then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between dichloromethane (DCM) (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to an orange solid which was applied to an SPE cartridge (silica, 20g). The cartridge was eluted sequentially with EtOAc : petrol (1:4, 1:2 and 1:1), then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 3 (0.165g). LCMS showed MH^+= 250; T_{RET} = 2.59 min.

Intermediate 4: Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous DMF (4ml) was treated with benzyl bromide (0.72g) then stirred vigorously and heated at 55°C for 4.5h. The mixture was allowed to cool, then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between DCM (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to a yellow oily solid which was dissolved in DCM and applied to an SPE cartridge (silica, 20g). The cartridge was eluted with a gradient of EtOAc : petrol (1:4, 1:2 and 1:1) then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 4 (0.33g). LCMS showed MH^+= 326; T_{RET} = 3.24 min.

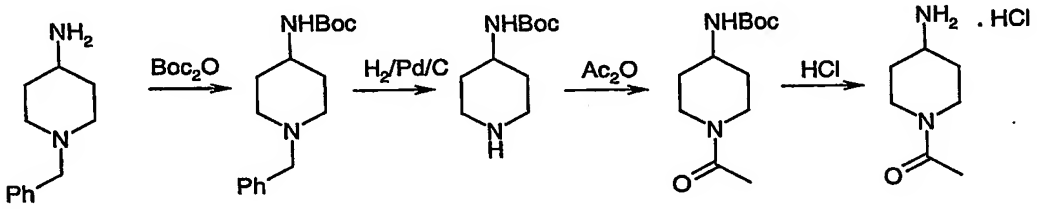
Intermediate 5: Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



A mixture of 5-amino-1-phenyl pyrazole (2.0g) and diethylethoxymethylene malonate (2.54ml) was heated under Dean Stark conditions at 120°C for 16h. The solution was cooled, phosphorus oxychloride (16ml) was then added and the mixture heated under reflux for a further 20h. Excess phosphorus oxychloride was removed in vacuo and the residue partitioned between diethyl ether and water, proceeding with extreme caution on addition of water. The ethereal layer was washed with further water, then dried over magnesium sulphate and concentrated in vacuo to afford ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (2.09g). LCMS showed MH^+= 302; T_{RET} = 3.80 min.

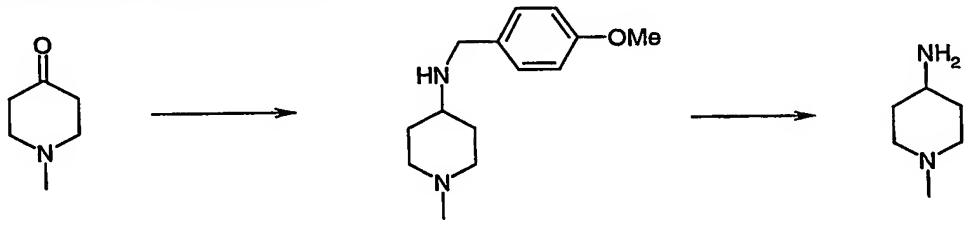
Intermediate 6: 1-Acetyl-4-aminopiperidine

Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:



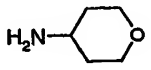
Intermediate 7: 1-Methyl-4-aminopiperidine

Prepared from commercially available N-methyl-4-piperidone as described by C. M. Andersson *et. al.* in WO01/66521:

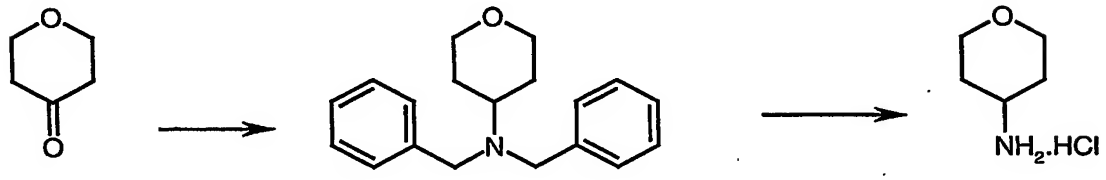


Intermediate 8: 4-Aminotetrahydropyran

Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126 (CAS 38041-19-9)



Intermediate 8A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride



Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine

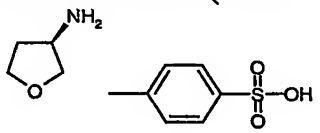
Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed MH^+= 282; T_{RET} = 1.98 min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

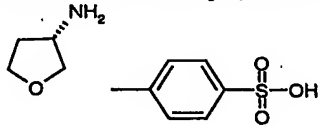
Intermediate 9: (R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate

Commercially available from Fluka Chemie AG (CAS 111769-27-8)



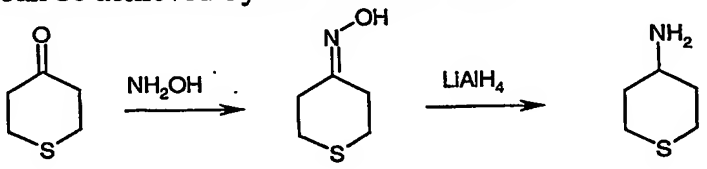
Intermediate 10: (S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate

Commercially available from E. Merck, Germany (CAS 104530-80-5)



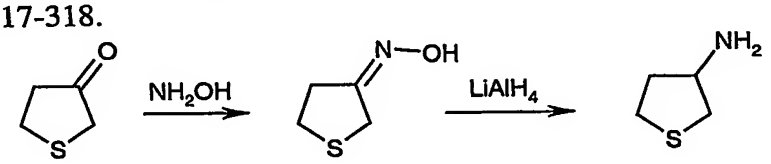
Intermediate 11: Tetrahydro-2H-thiopyran-4-amine

Prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



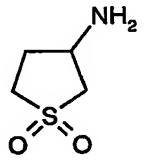
Intermediate 12: Tetrahydro-3-thiopheneamine

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



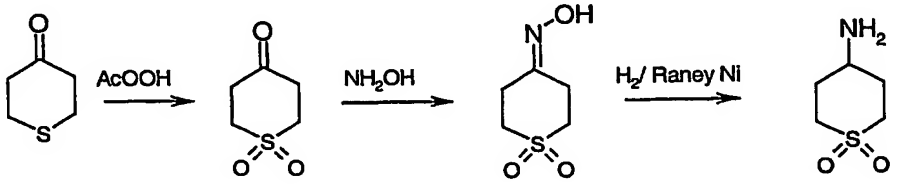
Intermediate 13: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride

Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

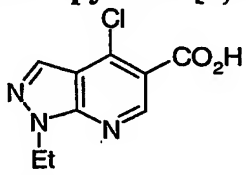


Intermediate 14: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. Oxidation to 1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.

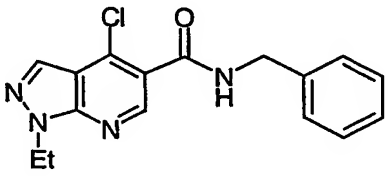


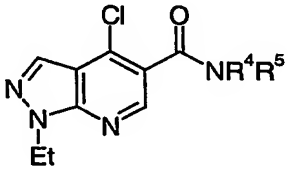
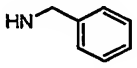
Intermediate 15: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 15 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 17: N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

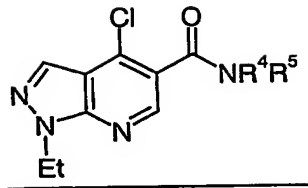


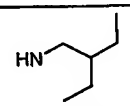
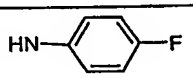
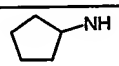
That is, Intermediate 17 is:  wherein NR^4R^5 = 

Intermediate 15 (3.5g) was dried over phosphorus pentoxide for 1h, then treated with thionyl chloride (47g). The mixture was stirred and heated at 75°C for 1.3h. Excess thionyl chloride was removed in vacuo and the residual oil azeotroped with dichloromethane (DCM) to afford **Intermediate 16**, presumed to be the acid chloride derivative of Intermediate 15, as a white solid (3.3g).

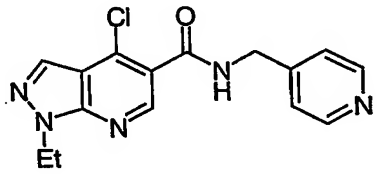
Intermediate 16 (0.473g) was dissolved in tetrahydrofuran (THF) (4ml) and treated with N,N-diisopropylethylamine (DIPEA) (0.509ml), then with benzylamine (0.209g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between dichloromethane and water. The layers were separated and the organics concentrated in vacuo to afford **Intermediate 17** (0.574g). LCMS showed $MH^+ = 315$; $T_{RET} = 2.90$min.

Similarly prepared were the following:



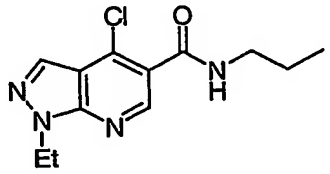
	NR^4R^5	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 18		2-Ethyl-N-butylamine	309	3.07
Intermediate 19		4-Fluoroaniline	319	3.08
Intermediate 20		Cyclopentylamine	293	2.76
Intermediate 21		Pyrrolidine	279	2.46

Intermediate 22: 4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



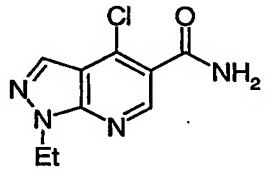
Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with diisopropylethylamine (DIPEA) (0.509ml), then with 4-(aminomethyl)pyridine (0.211g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo, then applied to an SPE cartridge (silica, 10g) which was eluted with a gradient of cyclohexane : EtOAc (2:1 increasing stepwise up to 0:1), followed by MeOH : EtOAc (5:95, then 10:90). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 22 (0.086g). LCMS showed $MH^+ = 316$; $T_{RET} = 1.84$min.

Intermediate 23: 4-Chloro-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



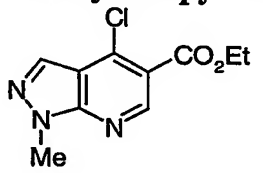
Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with DIPEA (0.509ml), then with n-propyl amine (0.115g) and the mixture stirred under nitrogen for 0.5h. A further portion of n-propyl amine (0.023g) was then added and stirring continued for 18h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo to afford Intermediate 23 (0.405g). LCMS showed $MH^+ = 267$; $T_{RET} = 2.54$min.

Intermediate 24: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



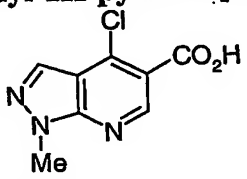
Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.30g) was dissolved in THF (3ml) and treated with a 0.5M solution of ammonia in dioxane (4.92ml). The mixture was stirred under nitrogen for 18h. A further portion of 0.5M ammonia in dioxane (4.92ml) was added and stirring continued for 72h. The mixture was concentrated in vacuo and the residue partitioned between DCM and 2M sodium hydroxide solution. The layers were separated and the organics concentrated to afford Intermediate 24 (0.278g). LCMS showed $MH^+ = 225$; $T_{RET} = 2.10$min.

Intermediate 25: Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



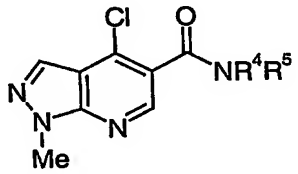
A mixture of 5-amino-1-methyl pyrazole (4.0g) and diethylethoxymethylene malonate (9.16ml) was heated at 150°C under Dean Stark conditions for 5h. Phosphorous oxychloride (55ml) was carefully added to the mixture and the resulting solution heated at 130°C under reflux for 18h. The mixture was concentrated in vacuo, then the residual oil cooled in an ice bath and treated carefully with water (100ml)(caution: exotherm). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The residual solid was purified by Biotage chromatography (silica, 90g), eluting with Et_20 : petrol (1:3). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 25 (4.82g). LCMS showed $MH^+ = 240$; $T_{RET} = 2.98$min

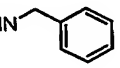
Intermediate 26: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 25 (4.0g) in dioxane (30ml) was treated with potassium hydroxide (7.54g) as a solution in water (20ml). The mixture was stirred for 16h, then diluted with water (150ml) and acidified to pH 3 with 5M aqueous hydrochloric acid. The mixture was stirred in an ice bath for 15min, then collected by filtration, washed with ice-cold water and dried in vacuo over phosphorous pentoxide to afford Intermediate 26 as a white solid (2.83g). LCMS showed $MH^+ = 212$; $T_{RET} = 2.26$min.

Intermediate 28: N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

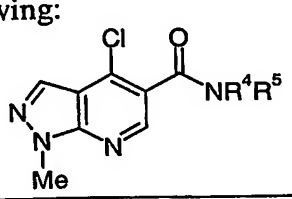


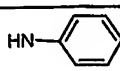
Intermediate 28 NR^4R^5 = 

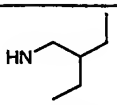
Intermediate 26 (2.5g) (previously dried over phosphorus pentoxide) was treated with thionyl chloride (25ml) and the mixture heated under reflux for 1h. Excess thionyl chloride was removed in vacuo to afford **Intermediate 27**, presumed to be the acid chloride derivative of Intermediate 26, as a white solid (2.7g).

Intermediate 27 (0.68g) was dissolved in THF (10ml) and treated with DIPEA (0.77ml), then with benzyl amine (0.339g) and the mixture stirred under nitrogen for 3h. The mixture was concentrated in vacuo, then partitioned between DCM (20ml) and water (10ml). The layers were separated and the organics concentrated in vacuo to afford **Intermediate 28** (0.90g). LCMS showed $MH^+ = 301$; $T_{RET} = 2.72$min.

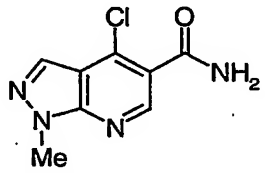
Similarly prepared were the following:



	NR^4R^5	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 29		4-Fluoroaniline	305	2.91

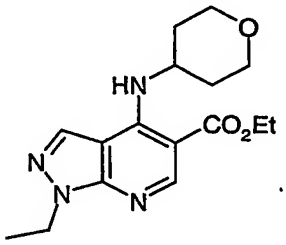
Intermediate 30		2-Ethyl-N-butylamine	295	2.97

Intermediate 31: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



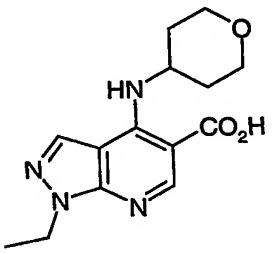
Acid chloride Intermediate 27 was synthesised from Intermediate 26 using the method shown above for Intermediate 28. Intermediate 27 (0.68g) was then treated with a 0.5M solution of ammonia in dioxane (17.7ml). Diisopropylethylamine (0.51ml) was then added and the mixture stirred for 21h. The mixture was then partitioned between DCM (100ml) and water (30ml). An insoluble solid was removed by filtration, washed with water (20ml) and dried in vacuo over phosphorous pentoxide to afford Intermediate 31 (0.544g). LCMS showed $MH^+ = 211$; $T_{RET} = 1.84$min.

Intermediate 32 (= Example 3): Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



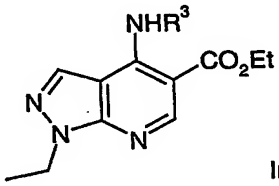
Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (0.088g) was added. The mixture was stirred under nitrogen, heated at 80°C for 16h, then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 32 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

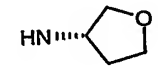
Intermediate 33: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 32 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50°C for 8h, then concentrated in vacuo, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 33 as an off-white solid (0.156g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

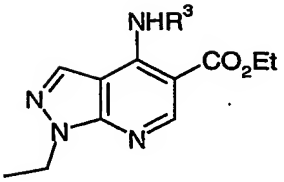
Intermediate 34: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

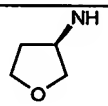
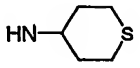
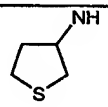
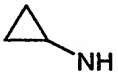


Intermediate 34 NHR^3 = 

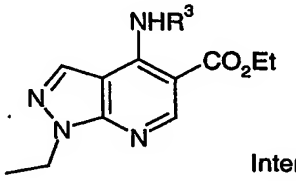
Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluenesulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 34 (0.052g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.70$min.

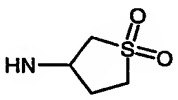
Similarly prepared were the following:



	NHR3	Amine Reagent	MH+ ion	T_{RET}(min)
Intermediate 35		(R)-(+)-3-Aminotetrahydrofuran 4-toluenesulphonate	305	2.73
Intermediate 36		Intermediate 11	335	3.21
Intermediate 37		Intermediate 12	321	3.10
Intermediate 38		Cyclopropylamine	275	2.98

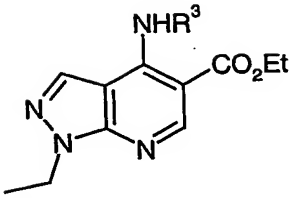
<u>Intermediate 39:</u> Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

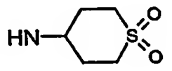


Intermediate 39 NHR³ = 

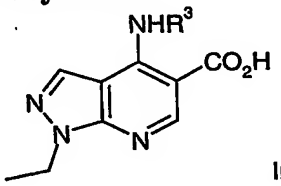
Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 39 (0.045g) as a mixture of enantiomers. LCMS showed $MH^+ = 353$; $T_{RET} = 2.60$min.

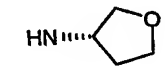
Similarly prepared was the following:



	NHR3	Amine Reagent	MH+ ion	TRET(min)
Intermediate 40		Intermediate 14	367	2.64

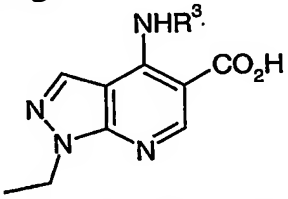
Intermediate 41: 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

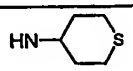


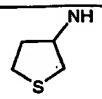
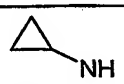
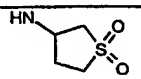
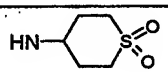
Intermediate 41 NHR3 = 

A solution of Intermediate 34 (0.037g) in ethanol : water (95:5, 3ml) was treated with sodium hydroxide (0.019g). The mixture was heated at 50°C for 16h, then concentrated in vacuo. The residue was dissolved in water (1.5ml) and acidified to pH 4 with acetic acid. The resultant white solid precipitate was removed by filtration and dried under vacuum. The filtrate was extracted with ethyl acetate and the organic layer collected and concentrated in vacuo to afford a further portion of white solid. The two solids were combined to afford Intermediate 41 (0.033g). LCMS showed MH^+ = 277; T_{RET} = 2.05 min.

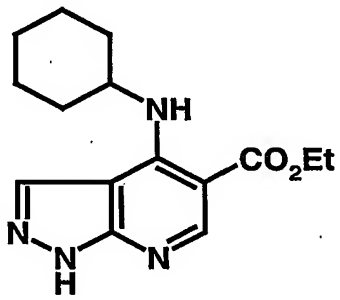
Similarly prepared were the following:



	NHR3	Starting material	MH+ ion	TRET(min)
Intermediate 42		Intermediate 35	277	2.05
Intermediate 43		Intermediate 36	307	2.40

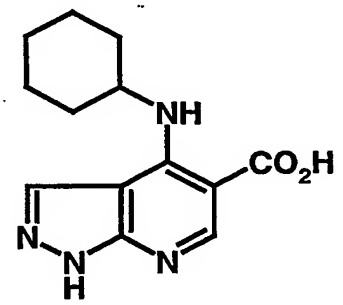
Intermediate 44		Intermediate 37	293	2.59
Intermediate 45		Intermediate 38	247	2.24
Intermediate 46		Intermediate 39	325	2.05
Intermediate 47		Intermediate 40	339	2.05

<u>Intermediate 48</u>: Ethyl 4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



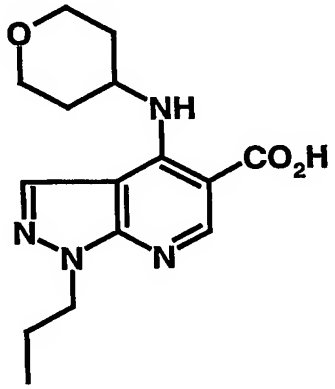
Intermediate 2 (0.69g) was suspended in cyclohexylamine (1.01ml), and the mixture was heated at 90 °C for 3h. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (25ml) and water (25ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (25ml) and the insoluble solid was collected and dried to afford Intermediate 48 as a beige solid (0.58g). LCMS showed MH^+=289; T_{RET} = 2.91min.

<u>Intermediate 49</u>: 4-(Cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



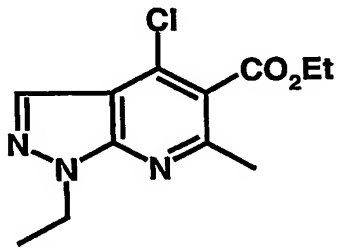
2M-Sodium hydroxide solution (0.5ml) was added to a stirred suspension of Intermediate 48 (0.2g) in dioxan (4ml) and water (0.5ml). After stirring overnight at room temperature, the reaction mixture was heated at 40 °C for 8h. A further quantity of 2M-sodium hydroxide solution (1.5ml) was added, and the reaction mixture was heated at 40 °C for 48h. The reaction solution was concentrated, diluted with water (10ml) and acidified with glacial acetic acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 49 (0.18g). LCMS showed $MH^+ = 261$; $T_{RET} =$ 2.09min.

Intermediate 50: 1-n-Propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



2M-Sodium hydroxide solution (0.7ml) was added to a stirred suspension of Example 185 (0.23g, described hereinafter) in ethanol (5ml) and water (1.5ml). After stirring overnight at room temperature, a further quantity of 2M-sodium hydroxide solution (0.7ml) was added, and the reaction mixture was heated at 43 °C for 2.5h. The reaction solution was concentrated, diluted with water (5ml) and acidified with 2M-hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 50 as a white solid (0.14g). LCMS showed $MH^+ = 305$; $T_{RET} =$ 2.42min.

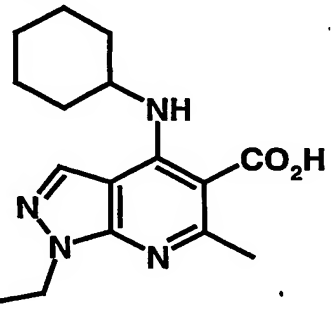
Intermediate 51: Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A mixture of 5-amino-1-ethylpyrazole (1.614g, 14.5mmol) and diethyl 2-(1-ethoxyethylidene)malonate (3.68g, 16.0mmol, as described by P.P.T. Sah, *J. Amer. Chem. Soc.*, 1931, 53, 1836) was heated at 150 °C under Dean Stark conditions for 5 hours. Phosphorous oxychloride (25ml) was carefully added to the mixture and the

resulting solution was heated at 130 °C under reflux for 18 hours. The mixture was concentrated *in vacuo*, then the residual oil was carefully added, with cooling, to water (100ml). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residual oil was purified by Biotage chromatography (silica, 90g) eluting with ethyl acetate-petrol (1:19). Fractions containing the desired product were combined and concentrated in vacuo to afford Intermediate 51 (1.15g). LCMS showed $MH^+ = 268$; $T_{RET} = 3.18$min.

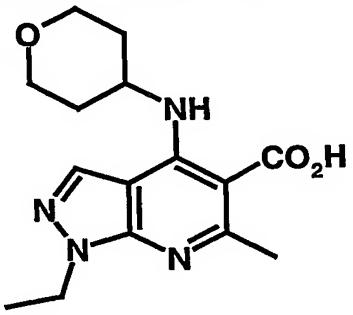
Intermediate 52: 4-(Cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



2M-Sodium hydroxide solution (0.39ml, 0.78mmol) was added to Example 190 (0.128g, 0.39mmol, described hereinafter) in ethanol (1.5ml), and the mixture was heated at 50 °C for 16 hours. The reaction mixture was concentrated, and the resulting aqueous solution was neutralised with 2M-hydrochloric acid to precipitate a solid which was collected by filtration. The filtrate was applied to an OASIS ® hydrophilic-lipophilic balance (HLB) Extraction cartridge * (1g) which was eluted with water followed by methanol. Evaporation of the methanol fraction gave a solid which was combined with the initial precipitated solid to afford Intermediate 52 (0.083g) as a white solid, presumed to be the carboxylic acid.

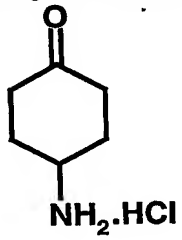
* OASIS ® HLB Extraction cartridges are available from Waters Corporation, 34 Maple Street, Milford, MA 01757, USA. The cartridges include a column containing a copolymer sorbent having a HLB such that when an aqueous solution is eluted through the column, the solute is absorbed or adsorbed into or onto the sorbent, and such that when organic solvent (e.g. methanol) is eluted the solute is released as an organic (e.g. methanol) solution. This is a way to separate the solute from aqueous solvent.

Intermediate 53: **1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Example 189 (0.248g, 0.75mmol, described hereinafter) in ethanol (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 53 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} =$ 1.86min.

Intermediate 54: **4-Aminocyclohexanone hydrochloride**



A solution of hydrogen chloride in dioxan (0.5ml, 2.0mmol, 4M) was added to a stirred solution of *tert*-butyl 4-oxocyclohexylcarbamate (0.043g, 0.20mmol, commercially available from Astatech Inc., Philadelphia, USA) in dioxan (0.5ml) and the mixture was stirred at room temperature. After 1h, the reaction mixture was evaporated to give Intermediate 54 as a cream solid (34mg). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.09 (br. s, 3H), 3.51 (tt, 11, 3.5Hz, 1H), 2.45 (m, 2H, partially obscured), 2.29 (m, 2H), 2.16 (m, 2H), 1.76 (m, 2H).

Table of Examples

Example Number	Name
1	Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
3	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
4	Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
6	Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
7	Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
8	Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
9	Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
10	Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
11	Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
12	Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
13	Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
14	Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
15	Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
16	Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
17	Ethyl 4-(cyclopentylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
18	Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)- 1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
19	Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
20	Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
21	N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
22	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

23	N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
24	4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
25	N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
26	N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
27	4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
28	N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine
29	N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine
30	1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine
31	4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
32	4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
33	1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
34	4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
35	4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
36	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
37	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
38	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
39	N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
40	N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
41	4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
42	4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
43	4-(Cyclohexylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
44	1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-

	b]pyridine-5-carboxamide
45	1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
46	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
47	4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
48	4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
49	1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
50	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
51	4-(Cyclopentylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
52	4-(Cyclohexylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
53	1-Ethyl-N-n-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
54	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
55	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
56	N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
57	4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
58	1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
59	N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
60	4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
61	N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
62	N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
63	N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
64	4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

65	4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
66	N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
67	4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
68	4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
69	N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
70	4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
71	4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
72	1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
73	N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
74	4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
75	N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
76	4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
77	N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
78	4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
79	1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
80	4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
81	1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
82	1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
83	1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
84	1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
85	N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
86	N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-

	b]pyridine-5-carboxamide
87	N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
88	N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
89	N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
90	N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
91	N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
92	1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
93	1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
94	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
95	1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
96	4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
97	4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
98	4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

Example No.	**Name**
100	1-Ethyl-*N*-[4-(methylsulfonyl)benzyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
101	*tert*-Butyl (1-{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperidin-3-yl)methylcarbamate
102	1-Ethyl-*N*-[3-(methylsulfonyl)benzyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
103	1-Ethyl-5-{[5-methoxy-6-(trifluoromethyl)-2,3-dihydro-1*H*-indol-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
104	*N*-[(5-Chloropyridin-2-yl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
105	*N*-(4-Chlorobenzyl)-1-ethyl-*N*-isopropyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

106	*N*-(3-Chlorobenzyl)-1-ethyl-*N*-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
107	1-Ethyl-*N*-[(5-methyl-3-phenylisoxazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
108	*N*-(2-*tert*-Butoxyethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
109	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(1,3-thiazol-2-ylmethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
110	1-Ethyl-*N*-(pyrimidin-4-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
111	1-Ethyl-*N*-[(2-methyl-1,3-thiazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
112	*N*-[3-(*tert*-Butoxymethyl)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
113	1-Ethyl-*N*-{2-[methyl(methylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
114	1-Ethyl-*N*-(pyrazin-2-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
115	1-Ethyl-5-{[4-(pyridin-2-ylcarbonyl)piperazin-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
116	*N*-(2-Chloro-6-fluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
117	1-Ethyl-*N*-[(6-oxo-1,6-dihydropyridin-3-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
118	*N*-[3-(Aminocarbonyl)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
119	1-Ethyl-*N*-{4-[(methylamino)carbonyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
120	1-Ethyl-*N*-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
121	*N*-{2-[(Anilinocarbonyl)amino]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
122	1-Ethyl-*N*-(1*H*-tetraazol-5-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide hydrochloride
123	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[2-(1*H*-1,2,4-triazol-1-yl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
124	*tert*-Butyl 2-[{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}(methyl)amino]ethylcarbamate
125	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[4-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
126	*tert*-Butyl 4-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)piperidine-1-carboxylate

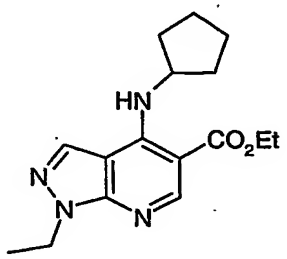
127	1-Ethyl-*N*-{3-[(methylsulfonyl)amino]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
128	*N*-[2-(Dimethylamino)benzyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
129	1-Ethyl-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
130	1-Ethyl-*N*-(tetrahydrofuran-2-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
131	1-ethyl-*N*-tetrahydro-2*H*-pyran-4-yl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
132	*N*-{4-[(Dimethylamino)sulfonyl]benzyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
133	1-Ethyl-*N*-{3-[(methylsulfonyl)amino]benzyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
134	1-{[1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperidine-2-carboxamide
135	1-Ethyl-*N*-(4-methoxyphenyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
136	1-Ethyl-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
137	1-Ethyl-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
138	1-Ethyl-*N*-(pyridin-3-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
139	1-Ethyl-*N*-(1-methylpiperidin-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
140	1-Ethyl-*N*-(1-ethylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
141	1-Ethyl-*N*-(2-piperidin-1-ylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
142	1-Ethyl-*N*-(3-morpholin-4-ylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
143	*N*-(3-Ethoxypropyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
144	*N*-(Cyclohexylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
145	*N*-[3-(Dimethylamino)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
146	1-Ethyl-*N*-neopentyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
147	1-ethyl-*N*-(4-methoxybenzyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

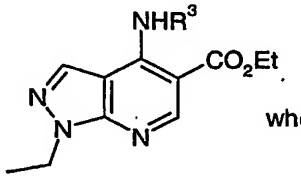
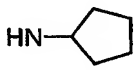
148	1-Ethyl-*N*-{2-[(phenylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
149	*N*-[2-(Acetylamino)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
150	1-Ethyl-*N*-{2-[(methylsulfonyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
151	1-Ethyl-*N*-methyl-*N*-(pyridin-4-ylmethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
152	1-Ethyl-*N*-{2-[(2-methoxyphenyl)(methyl)amino]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
153	1-Ethyl-*N*-(2-oxo-2-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1H-pyrazolo[3,4-*b*]pyridine-5-carboxamide
154	*N*-(2,5-Difluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
155	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
156	*N*,1-Diethyl-*N*-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
157	*N*-Cyclopropyl-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
158	N-(2-amino-2-oxoethyl)-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
159	1-Ethyl-*N*-(3-methoxyphenyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
160	*N*-(3,4-Difluorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
161	Ethyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)propanoate
162	*N*-(1-Benzylpiperidin-4-yl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
163	*N*-Butyl-4-{[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}piperazine-1-carboxamide
164	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(1,3,4-thiadiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
165	*N*-(2,3-Dihydro-1*H*-inden-2-yl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
166	1-Ethyl-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
167	*N*-(3,4-Dimethoxybenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
168	*N*-(3-Chlorobenzyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

169	1-Ethyl-5-[(4-methylpiperazin-1-yl)carbonyl]-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
170	1-Ethyl-*N*-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
171	1-Ethyl-5-{[4-(4-methoxyphenyl)piperazin-1-yl]carbonyl}-*N*-tetrahydro-2*H*-pyran-4-yl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine
172	1-Ethyl-*N*-{4-[(methylsulfonyl)methyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
173	N-[3-(dimethylamino)-3-oxopropyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
174	1-Ethyl-*N*-[(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
175	1-Ethyl-*N*-{4-[(methylamino)sulfonyl]phenyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
176	*N*-(2-Cyanoethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
177	1-Ethyl-*N*-methyl-*N*-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
178	1-Ethyl-*N*-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
179	1-Ethyl-*N*-methyl-*N*-[(1-methyl-1*H*-imidazol-2-yl)methyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
180	1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2-thien-2-ylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
181	*N*-[2-(4-Chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
182	1-Ethyl-*N*-[2-(2-methoxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
183	Ethyl 4-(cyclohexylamino)-1-(3-ethoxy-3-oxopropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
184	*N*-Benzyl-4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
185	Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
186	Ethyl 1-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
187	N-[4-(Methylsulfonyl)benzyl]-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-b]pyridine-5-carboxamide
188	N-(4-Fluorophenyl)-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

189	Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
190	Ethyl 4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
191	4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
192	*N*-Benzyl-4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
193	4-(Cyclohexylamino)-1-ethyl-*N*-(4-fluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
194	4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
195	4-(Cyclohexylamino)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
196	*N*-Benzyl-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
197	*N*-Benzyl-1-ethyl-4-[(2-oxoazepan-3-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
198	*N*-Benzyl-1-ethyl-4-[(3-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide; also called *N*-benzyl-1-ethyl-4-[(3-hydroxycyclohexan-1-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
199	*N*-Benzyl-1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide; also called *N*-benzyl-1-ethyl-4-[(4-hydroxycyclohexan-1-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
200	*N*-Benzyl-1-ethyl-4-[(3-hydroxycyclopentyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide; also called *N*-benzyl-1-ethyl-4-[(3-hydroxycyclopentan-1-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
201	*N*-Benzyl-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide; also called *N*-Benzyl-1-ethyl-4-[(4-oxocyclohexan-1-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
202	1-Ethyl-*N*-(2-hydroxy-1-methylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
203	Methyl (2*S*)-2-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-hydroxypropanoate

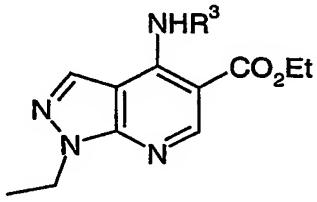
Example 1: Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

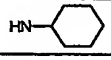
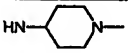
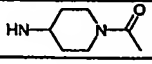


That is, Example 1 is  where NHR^3 = 

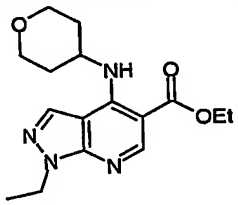
Intermediate 1 (0.051g) and cyclopentyl amine (0.019g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was loaded directly onto an solid phase extraction (SPE) cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O, (v) EtOAc, (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Example 1 (0.074g). LCMS showed $MH^+ = 303$; $T_{RET} = 3.45$min.

Similarly prepared were the following:



	NHR^3	Amine reagent	MH^+ ion	T_{RET}(min)
Example 2		Cyclohexyl amine	317	3.65
Example 3		4-Amino tetrahydropyran	319	2.93
Example 4		Intermediate 7	332	2.17
Example 5		Intermediate 6	360	3.20

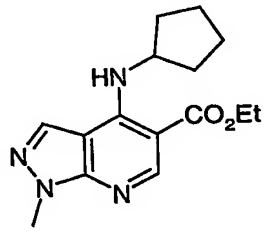
Example 3 (=Intermediate 32): Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Instead of the method shown above (called Method A), the compound of Example 3 can also be made using the following method:

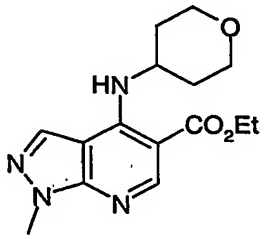
Example 3, Method B: Intermediate 1 (2.5g) was dissolved in acetonitrile (15ml). 4-Aminotetrahydropyran hydrochloride (1.1g) and N,N-diisopropylethylamine (9.4ml) were added and the mixture stirred under nitrogen at 85°C for 16h. A trace of starting material remained, so an additional portion of 4-aminotetrahydropyran hydrochloride (0.11g) was added and stirring continued at 85°C for a further 16h. The mixture was then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was washed with further water (2x20ml) then dried (Na_2SO_4) and concentrated in vacuo. The residue was further purified by chromatography using Biotage (silica, 90g), eluting with cyclohexane : ethyl acetate to afford Example 21 (2.45g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.90$min.

Example 6: Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



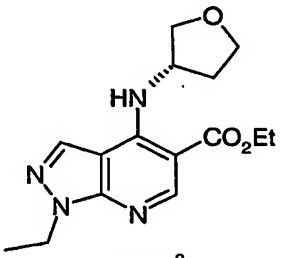
Intermediate 3 (0.045g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.07ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was evaporated to a brown solid, which was purified by mass directed autoprep HPLC, to afford Example 6 as a white solid (0.008g). LCMS showed $MH^+ = 289$; $T_{RET} = 3.22$ min.

Example 7: Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

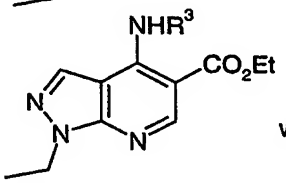


Intermediate 3 (0.035g) was placed in a Reactivial™ and treated with 4-amino tetrahydropyran (0.06ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate. The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 7 as a white solid (0.008g). LCMS showed MH^+= 305; T_{RET} = 2.67 min.

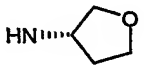
Example 8: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



that is:

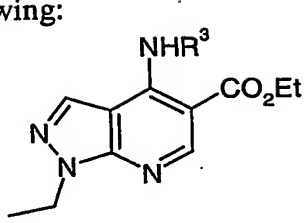


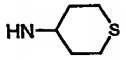
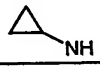
where NHR^3 =



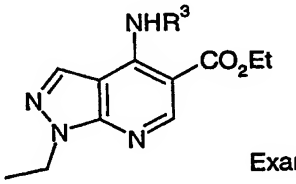
Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluene sulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 8 (0.052g). LCMS showed MH^+ = 305; T_{RET} = 2.70min.

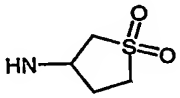
Similarly prepared were the following:



	NHR^3	Amine Reagent	MH^+ ion	T_{RET}(min)
Example 9		(R)-(+)-3-Aminotetrahydrofuran 4-toluene sulphonate	305	2.73
Example 10		Intermediate 11	335	3.21
Example 11 (mixture of enantiomers)		Intermediate 12	321	3.10
Example 12		Cyclopropyl amine	275	2.98

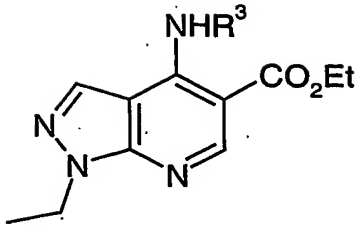
<u>Example 13:</u> Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

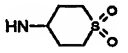


Example 13 NHR^3 = 

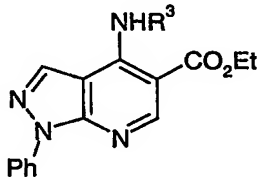
Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 13 (0.045g) as a mixture of enantiomers. LCMS showed $MH^+ = 353$; $T_{RET} = 2.60$min.

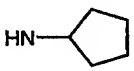
Similarly prepared was the following:



	NHR^3	Amine Reagent	MH$^+$ ion	T_{RET}(min)
Example 14		Intermediate 14	367	2.64

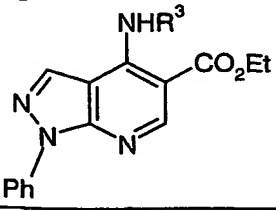
<u>Example 15:</u> Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



Example 15 NHR^3 = 

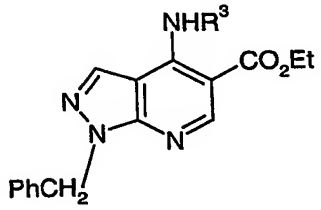
Intermediate 5 (0.02g) and cyclopentyl amine (0.007ml) were suspended in ethanol (1ml) and triethylamine (0.046ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 18h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between chloroform (1ml) and water (0.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of Et_2O : cyclohexane; (0:1 then 1:8, 1:5, 1:3, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 15 (0.024g). LCMS showed MH$^+$ = 351; T_{RET} = 4.19min.

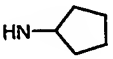
Similarly prepared was the following:



NHR^3	Amine Reagent	Product	MH$^+$ ion	T_{RET}(min)
	4-Amino tetrahydropyran	Example 16	367	3.58

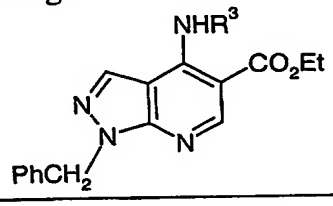
Example 17: Ethyl 4-(cyclopentylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

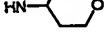


Example 17 NHR^3 = 

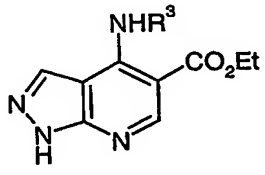
Intermediate 4 (0.04g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied as a solution in chloroform to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate : petrol (1:2). The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 17 as a white solid (0.013g). LCMS showed MH^+= 365; T_{RET} = 3.69 min.

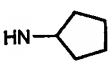
Similarly prepared was the following:



	NHR^3	Amine reagent	MH^+ ion	T_{RET}(min)
Example 18		4-Amino tetrahydropyran	381	3.28

Example 19: Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

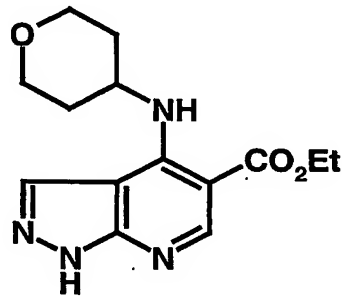


Example 19 NHR^3 = 

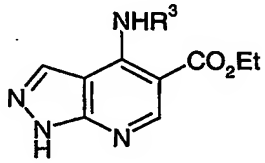
Intermediate 2 (0.035g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room

temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The residual solid was triturated with Et_2O and the insoluble off-white solid collected and air-dried to afford Example 19 (0.016g). LCMS showed $MH^+ = 275$; $T_{RET} = 2.58$ min.

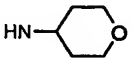
Example 20: Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



that is:



Example 20 NHR^3 =

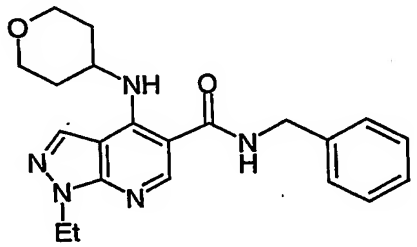


Intermediate 2 (0.035g) was placed in a Reactivial™ and treated with 4-aminotetrahydropyran (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The crude product was purified by mass directed autoprep HPLC to afford Example 20 as an off-white solid (0.011g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.08$ min.

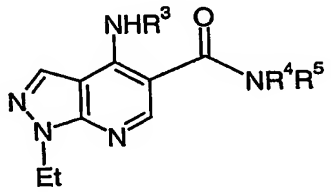
Alternative synthetic method for Example 20:

Intermediate 2 (2g) was suspended in 4-aminotetrahydropyran (2g), and the mixture was heated at 90 °C for 6h. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (50ml) and water (50ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (30ml) and the insoluble solid was collected and dried to afford Example 20 as a cream solid (2.24g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.19$min.

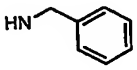
Example 21: **N-benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**



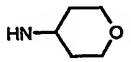
that is, Example 21 is:



wherein NR^4R^5 =



NHR^3 =



Three alternative methods, A, B and C, have been used to make Example 21, as follows:

Example 21, Method A:

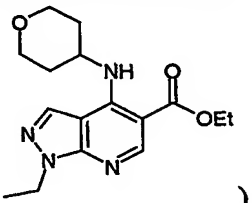
A solution of the 4-chloro Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1.9ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of 4-aminotetrahydropyran (Intermediate 8, 1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of 4-amino-tetrahydropyran (0.01ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in dichloromethane (DCM), then applied to an solid phase extraction (SPE) cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were concentrated in vacuo to afford Example 21 (0.004g). LCMS showed $MH^+ = 380$; $T_{RET} = 2.92$min.

Example 21 , Method B:

Intermediate 17 (0.031g, 0.1 mmol) was dissolved in acetonitrile (1ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 8A, 0.015g, 0.11 mmol) and N,N-diisopropylethylamine (0.08ml, 0.5 mmol) were added and the mixture stirred under nitrogen at 85°C for 16h, then concentrated in vacuo. The residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was concentrated in vacuo to afford Example 21 (0.027g). LCMS showed $MH^+ = 380$; $T_{RET} = 2.92$ min.

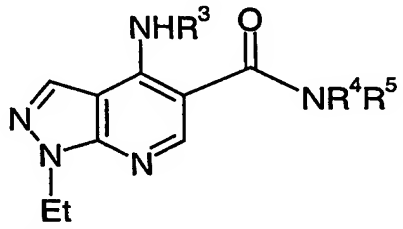
Example 21 , Method C:

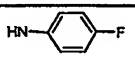
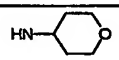
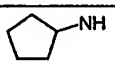
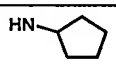
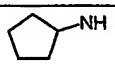
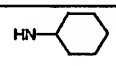
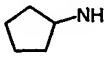
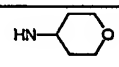
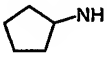
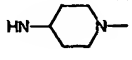
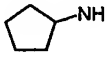
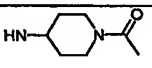
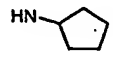
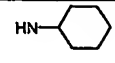
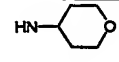
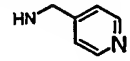
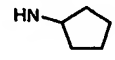
This alternative route C to Example 21 involves formation of the ester of Example 3 =

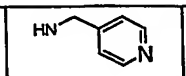
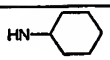
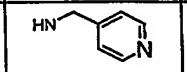
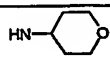
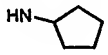
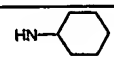
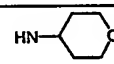
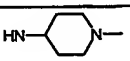
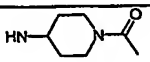


Intermediate 32 ( ) using one of the methods described above, conversion of the ester of Example 3 / Intermediate 32 into the carboxylic acid (Intermediate 33) using the method given above for Intermediate 33, and then amide bond formation to form Example 21 using the method of Examples 81-84 below.

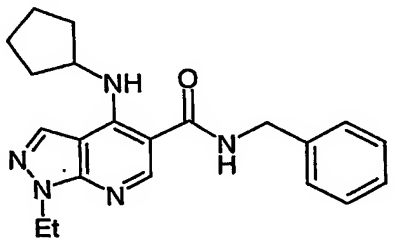
The following compounds can be similarly prepared using one or more of Methods A, B or C above, preferably Method A or B:



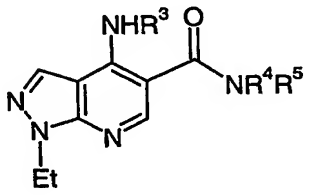
	NR^4R^5	NHR^3	Starting Material	Amine Reagent	MH^+ ion	T_{RET} (min)
Example 22			Intermediate 19	4-amino tetrahydropyran	384	3.09
Example 23			Intermediate 20	Cyclopentyl amine	342	3.29
Example 24			Intermediate 20	Cyclohexyl amine	356	3.47
Example 25			Intermediate 20	4-amino tetrahydropyran	358	2.79
Example 26			Intermediate 20	Intermediate 7	371	2.16
Example 27			Intermediate 20	Intermediate 6	400	2.64
Example 28			Intermediate 21	Cyclopentyl amine	328	2.69
Example 29			Intermediate 21	Cyclohexyl amine	342	2.87
Example 30			Intermediate 21	4-amino tetrahydropyran	344	2.33
Example 31			Intermediate 22	Cyclopentyl amine	365	2.38

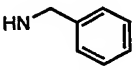
Example 32			Intermediate 22	Cyclohexyl amine	379	2.54
Example 33			Intermediate 22	4-amino tetrahydropyran	381	2.09
Example 34	NH_2		Intermediate 24	Cyclopentyl amine	274	2.59
Example 35	NH_2		Intermediate 24	Cyclohexyl amine	288	2.79
Example 36	NH_2		Intermediate 24	4-amino tetrahydropyran	290	2.22
Example 37	NH_2		Intermediate 24	Intermediate 7	303	1.81
Example 38	NH_2		Intermediate 24	Intermediate 6	331	2.06

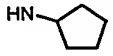
<u>Example 39:</u> N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 39 is:



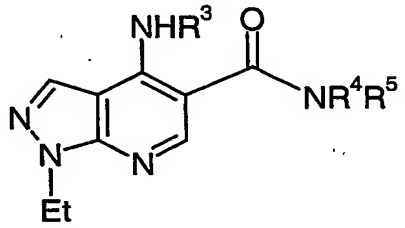
wherein NR^4R^5 = 

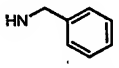
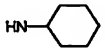
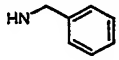
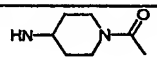
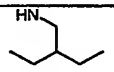
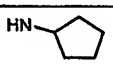
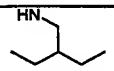
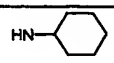
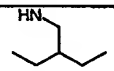
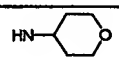
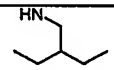
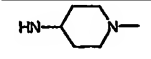
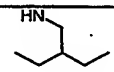
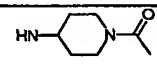
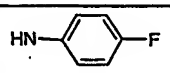
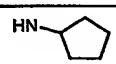
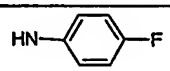
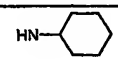
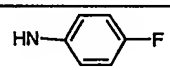
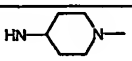
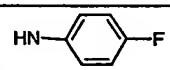
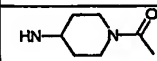
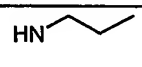
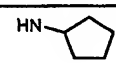
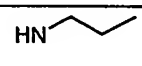
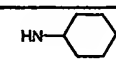
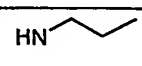
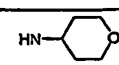
NHR^3 = 

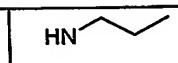
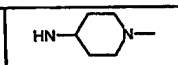
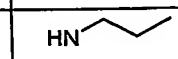
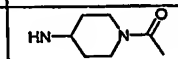
A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of cyclopentyl amine (0.009ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et_2O, (iii) EtOAc and (iv) MeOH.

Fractions containing desired material were combined to afford Example 39 (0.007g). LCMS showed $MH^+ = 364$; $T_{RET} = 3.38$min.

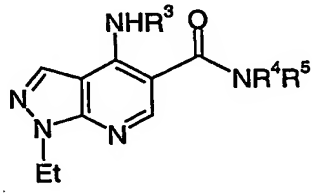
Similarly prepared were the following:

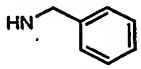


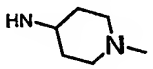
	NR^4R^5	NHR^3	Starting Material	Amine reagent	MH^+ ion	T_{RET} (min)
Example 40			Intermediate 17	Cyclohexyl amine	378	3.43
Example 41			Intermediate 17	Intermediate 6	421	2.75
Example 42			Intermediate 18	Cyclopentyl amine	358	3.63
Example 43			Intermediate 18	Cyclohexyl amine	372	3.79
Example 44			Intermediate 18	4-amino tetrahydro-pyran	374	3.13
Example 45			Intermediate 18	Intermediate 7	387	2.37
Example 46			Intermediate 18	Intermediate 6	415	2.92
Example 47			Intermediate 19	Cyclopentyl amine	368	3.61
Example 48			Intermediate 19	Cyclohexyl amine	382	3.76
Example 49			Intermediate 19	Intermediate 7	397	2.29
Example 50			Intermediate 19	Intermediate 6	425	2.88
Example 51			Intermediate 23	Cyclopentyl amine	316	3.05
Example 52			Intermediate 23	Cyclohexyl amine	330	3.26
Example 53			Intermediate 23	4-amino tetrahydro-pyran	332	2.58

Example 54			Intermediate 23	Intermediate 7	345	1.94
Example 55			Intermediate 23	Intermediate 6	373	2.46

<u>Example 56:</u> N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

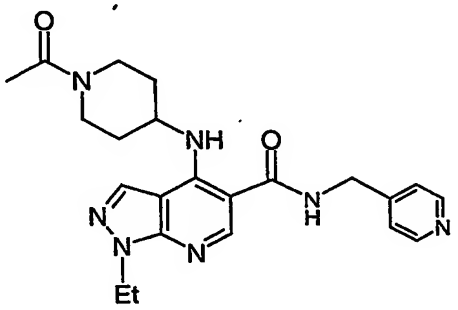


Example 56 NR^4R^5 = 

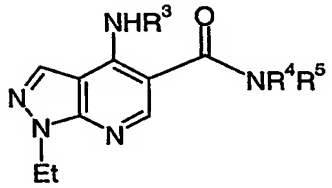
NHR^3 = 

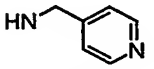
A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 7 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of Intermediate 7 (0.01ml of undiluted amine) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et_2O, (iii) EtOAc and (iv) MeOH. The methanol fraction was concentrated and further purified by SPE (silica, 0.5g) eluting with (I) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 56 (0.004g). LCMS showed MH^+ = 393; T_{RET} = 2.26min.

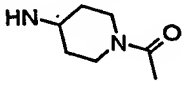
Example 57: 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 57 is:



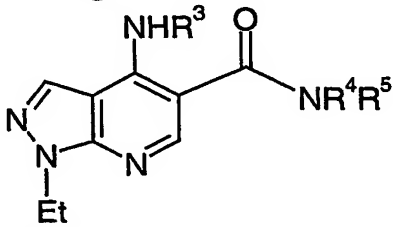
wherein NR^4R^5 = 

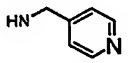
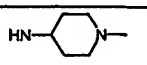
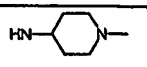
NHR^3 = 

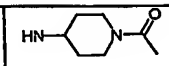
A solution of Intermediate 22 (0.03g, *ca.* 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 6 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of Intermediate 6 (0.01ml, undiluted) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol.

The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) eluting with (I) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 57 (0.003g). LCMS showed $MH^+ = 422$; $T_{RET} = 2.1$min.

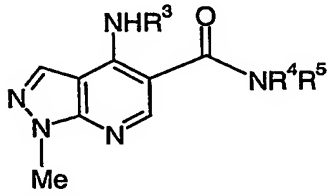
Similarly prepared were the following:



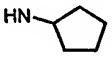
	NR^4R^5	NHR^3	Starting Material	Amine reagent	MH^+ ion	T_{RET} (min)
Example 58			Intermediate 22	Intermediate 7	394	1.66
Example 59			Intermediate 21	Intermediate 7	357	1.94

Example 60			Intermediate 21	Intermediate 6	385	2.3

Example 61: N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

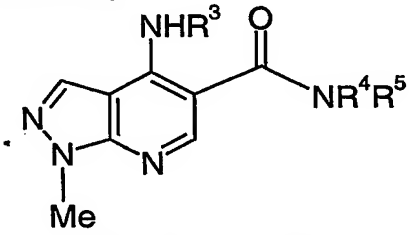


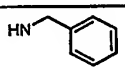
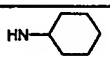
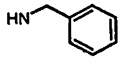
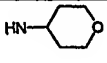
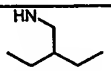
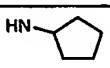
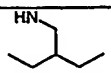
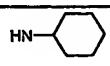
Example 61 NR^4R^5 = 

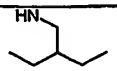
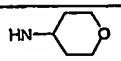
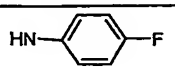
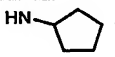
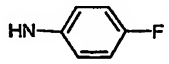
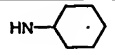
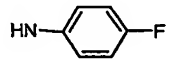
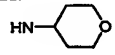
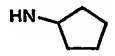
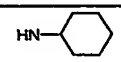
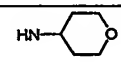
NHR^3 = 

A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of cyclopentyl amine (0.009ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were combined to afford Example 61 (0.039g). LCMS showed $MH^+ = 350$; T_{RET} = 2.88min.

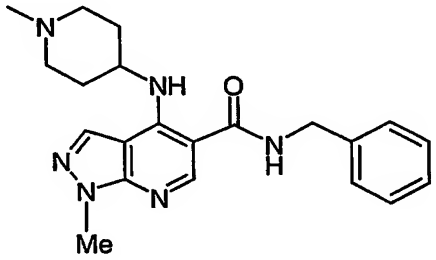
Similarly prepared were the following:



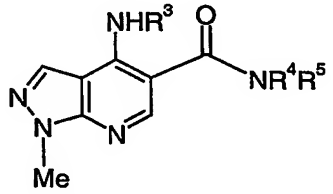
	NR^4R^5	NHR^3	Starting Material	Amine Reagent	MH^+ ion	T_{RET} (min)
Example 62			Intermediate 28	Cyclohexyl amine	364	3.05
Example 63			Intermediate 28	4-amino tetrahydropyran	366	2.52
Example 64			Intermediate 30	Cyclopentyl amine	344	3.06
Example 65			Intermediate 30	Cyclohexyl amine	358	3.23

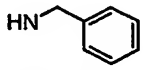
Example 66			Intermediate 30	4-amino tetrahydropyran	360	2.69
Example 67			Intermediate 29	Cyclopentyl amine	354	3.17
Example 68			Intermediate 29	Cyclohexyl amine	368	3.33
Example 69			Intermediate 29	4-amino tetrahydropyran	370	2.72
Example 70	NH_2		Intermediate 31	Cyclopentyl amine	260	2.10
Example 71	NH_2		Intermediate 31	Cyclohexyl amine	274	2.29
Example 72	NH_2		Intermediate 31	4-amino tetrahydropyran	276	1.86

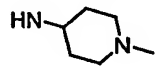
Example 73: N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 73 is:



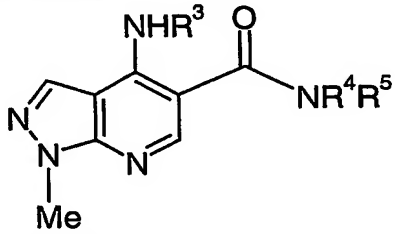
wherein NR^4R^5 = 

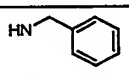
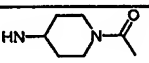
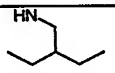
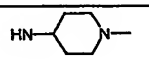
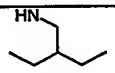
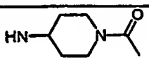
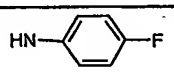
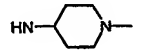
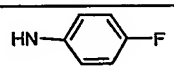
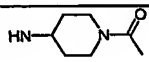
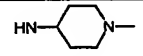
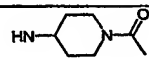
NHR^3 = 

A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of Intermediate 7 (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of Intermediate 7 (0.01ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were

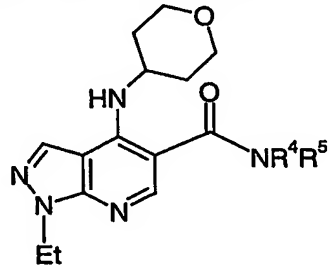
combined and concentrated in vacuo. The residue was further purified by SPE (silica, 0.5g) eluting with (i) DCM, (ii) chloroform, (iii) EtOAc and (iv) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 73 (0.029g). LCMS showed $MH^+ = 379$; $T_{RET} = 2.05$min.

Similarly prepared were the following:



	NR^4R^5	NHR^3	Starting Material	Amine Reagent	MH^+ ion	T_{RET} (min)
Example 74			Intermediate 28	Intermediate 6	407	2.57
Example 75			Intermediate 30	Intermediate 7	373	2.20
Example 76			Intermediate 30	Intermediate 6	401	2.74
Example 77			Intermediate 29	Intermediate 7	383	2.12
Example 78			Intermediate 29	Intermediate 6	411	2.69
Example 79	NH_2		Intermediate 31	Intermediate 7	289	1.64
Example 80	NH_2		Intermediate 31	Intermediate 6	317	1.99

<u>Example 81</u>: 1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

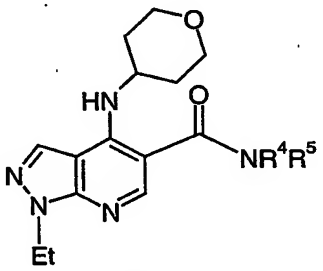


Example 81 NR^4R^5 = NHMe

To a stirred suspension of Intermediate 33 (0.025g, ca. 0.08 to 0.09 mmol) in chloroform (2ml) was added thionyl chloride (0.025ml) and the mixture stirred at room temperature

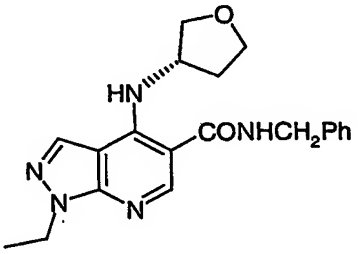
for 1h. The mixture was cooled to 0°C and methylamine added (2M solution in THF, 0.69ml = 1.38 mmol). After returning to room temperature the mixture was stirred for a further 1h, then quenched by addition of water (4ml) and the layers separated. The organic layer was concentrated then applied to an SPE cartridge (silica, 1g) which was eluted with (i) DCM, (ii) Et_2O (2:1), (iii) EtOAc, (iv) MeOH: EtOAc (1:9). Fractions containing desired material were combined to afford Example 81 (0.019g). LCMS showed $MH^+ = 304$; $T_{RET} = 2.19$min.

Similarly prepared:

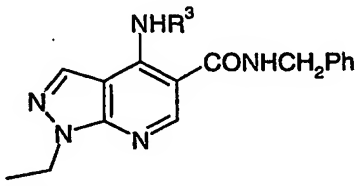


	NR^4R^5	Amine reagent	MH^+ ion	T_{RET} (min)
Example 82	NMe_2	Dimethylamine (2M in THF)	318	2.06
Example 83	NHEt	Ethylamine (2M in THF)	318	2.31
Example 84	NH^iPr	Isopropylamine (2M in THF)	332	2.44

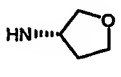
Example 85: N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



That is, Example 85 is:



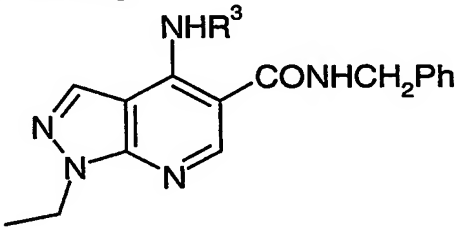
wherein NHR^3 =

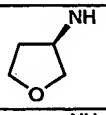
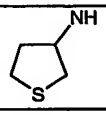
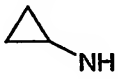
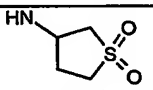
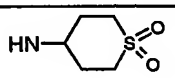


Intermediate 41 (0.017g, 0.062 mmol) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for

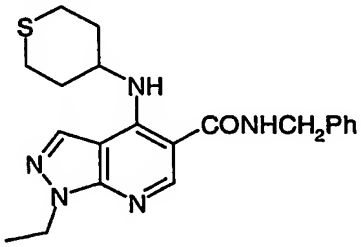
10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer was applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1, 2:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 85 (0.017g). LCMS showed $MH^+ = 366$; $T_{RET} = 2.80$min.

Similarly prepared were the following:



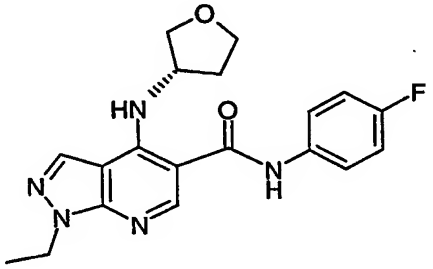
	NHR3	Starting material	MH^+ ion	T_{RET} (min)
Example 86		Intermediate 42	366	2.80
Example 87		Intermediate 44	382	3.11
Example 88		Intermediate 45	336	3.00
Example 89		Intermediate 46	414	2.69
Example 90		Intermediate 47	428	2.75

<u>Example 91:</u> N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

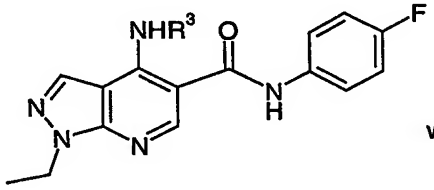


Intermediate 43 (0.019g) was dissolved in DMF (2ml), then treated with HATU (0.024g) followed by diisopropylethyl amine (0.022ml) and the mixture stirred for 10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 91 (0.023g). LCMS showed $MH^+ = 396$; $T_{RET} = 3.26$min.

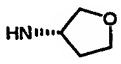
<u>Example 92:</u> 1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 92 is:

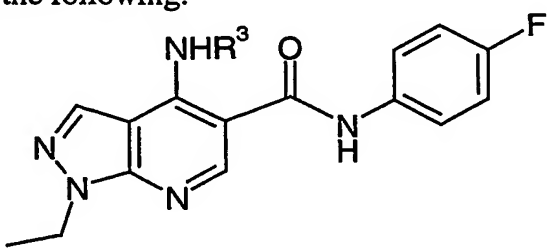


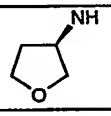
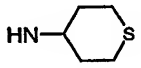
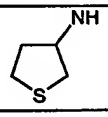
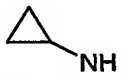
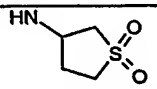
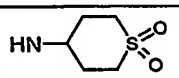
wherein NHR^3 =



Intermediate 41 (0.017g) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for 10 min. 4-Fluoroaniline (0.006ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer concentrated in vacuo. The crude mixture was purified by mass directed autoprep HPLC to afford Example 92 (0.013g). LCMS showed $MH^+ = 370$; $T_{RET} = 2.91$min.

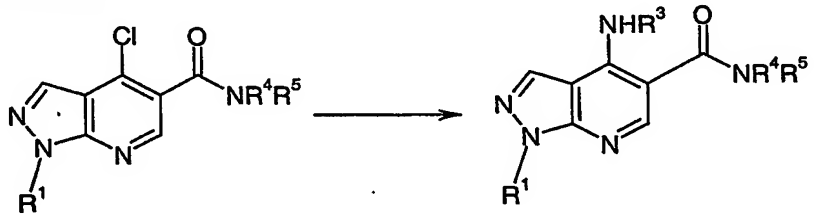
Similarly prepared were the following:



	NHR^3	Starting material	MH^+ ion	T_{RET} (min)
Example 93		Intermediate 42	370	2.91
Example 94		Intermediate 43	400	3.37
Example 95		Intermediate 44	386	3.27
Example 96		Intermediate 45	340	3.21
Example 97		Intermediate 46	418	2.80
Example 98		Intermediate 47	432	2.84

Example 99

In all of Examples 22 to 98, where a 4-amino 5-carboxamide Example of the following Formula I has been synthesised from the 4-chloro derivative, then an alternative final-step synthesis is as follows:

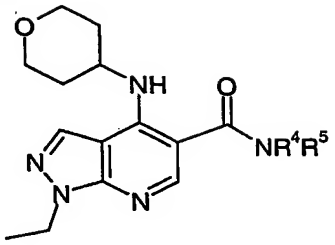


Formula IV

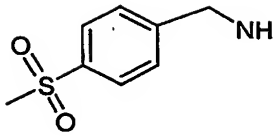
Formula I

An intermediate of Formula IV above (0.1mmol) was dissolved in acetonitrile (1ml). An amine of formula R^3NH_2 (0.11mmol, 1.1 mole equivalents) and N,N-diisopropylethylamine (0.5mmol, 5 mole equivalents) were added and the mixture stirred under nitrogen at 85°C for 16h. After concentration in vacuo, the residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was concentrated in vacuo to afford an Example of Formula I.

Example 100

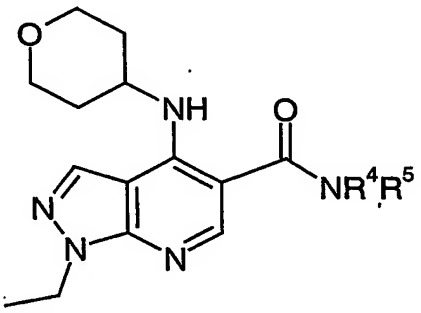


Example 100 NR^4R^5 =

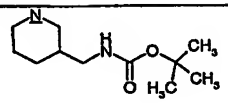
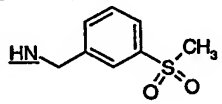
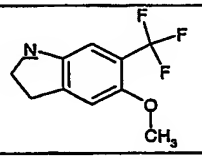
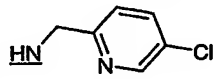
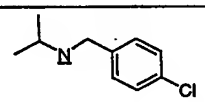
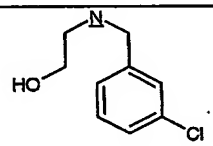
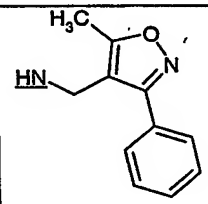
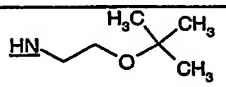
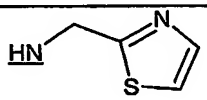
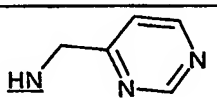
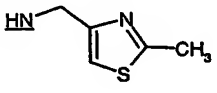


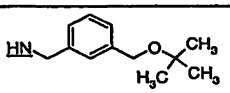
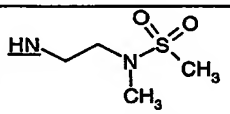
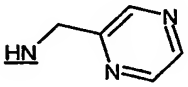
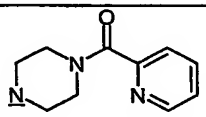
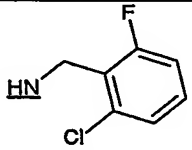
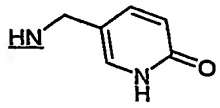
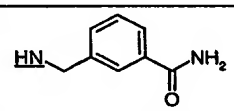
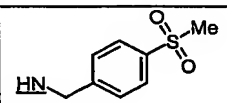
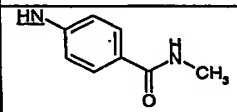
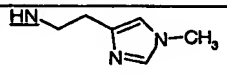
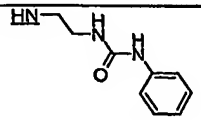
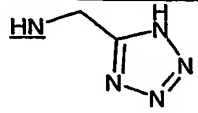
Intermediate 33 (0.048mmol) was dissolved in DMF (0.5ml), then treated with HATU (0.048mmol) followed by diisopropylethyl amine (0.096mmol) and the mixture stirred for 10 min. 4-Methylsulfonylbenzylamine (0.052mmol, available from Acros Organics) was then added and stirring continued for a further 16 hours. The mixture was concentrated *in vacuo*. The crude mixture was purified by mass directed autoprep HPLC to afford Example 100 (0.013g). LCMS showed $MH^+ = 458$; $T_{RET} = 2.22$min.

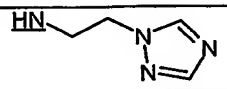
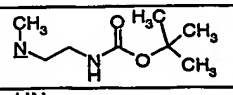
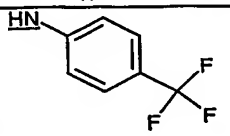
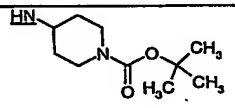
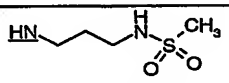
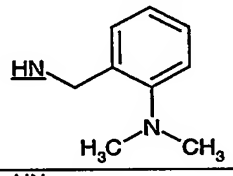
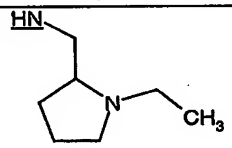
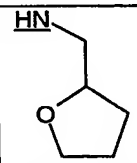
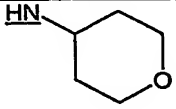
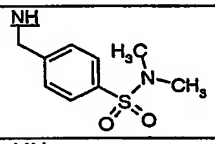
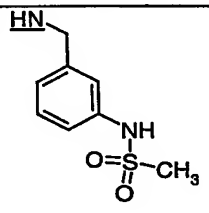
Similarly prepared, but replacing the 4-methylsulfonylbenzylamine with the same or similar number of moles of another amine R^4R^5NH, were the following compounds:

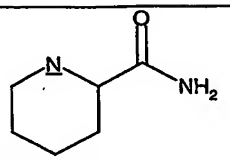
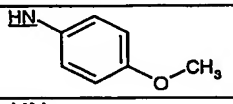
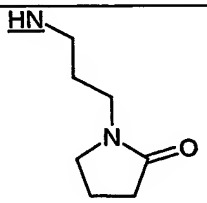
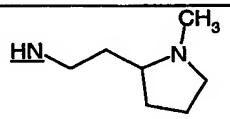
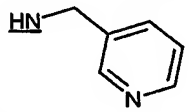
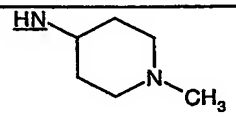
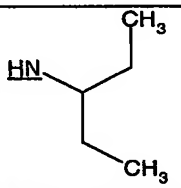
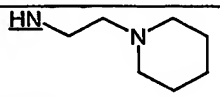
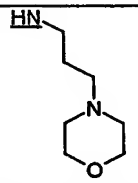
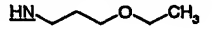
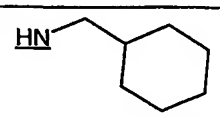
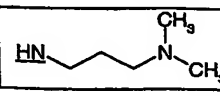


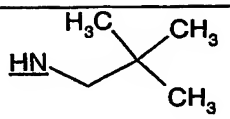
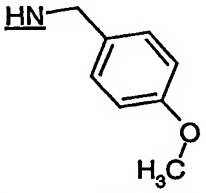
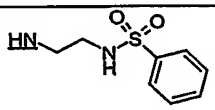
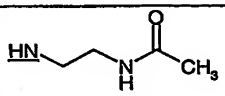
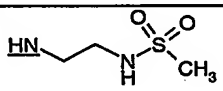
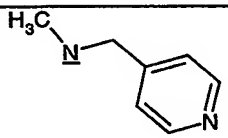
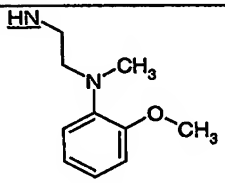
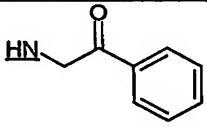
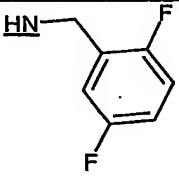
	NR^4R^5 (the N atom linking R^4 and R^5 to the –CO-pyrazolo-pyridine moiety is underlined)	**Source of R^4R^5NH**	**Starting Material**	**MH $^+$ ion**	**T_{RET} (min)**

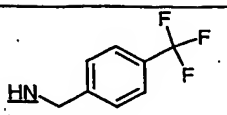
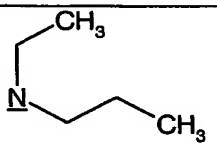
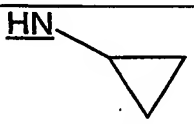
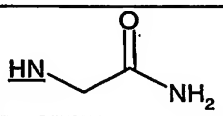
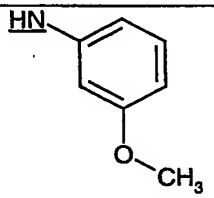
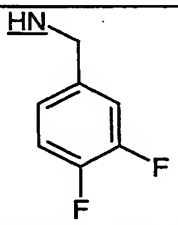
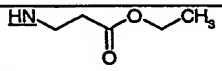
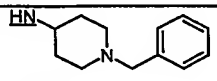
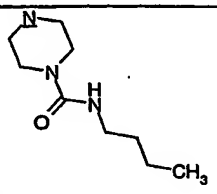
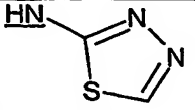
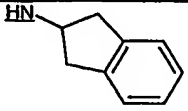
Example 101		AstaTech, Inc. 8301 Torresdale Ave. Philadelphia, PA, 19136 USA	Intermediate 33	487	2.29
Example 102		J. Chem. Soc., 1945, 633	Intermediate 33	458	2.2
Example 103		WO 98/52943	Intermediate 33	490	2.66
Example 104		J. Org. Chem., 1979, 44(3), 396	Intermediate 33	415	2.28
Example 105		Seriya Khimicheskaya, 1989, (7), 1694	Intermediate 33	456	2.65
Example 106		SALOR (Aldrich)	Intermediate 33	458	2.32
Example 107		Maybridge Chemical Company Ltd. Trevillett Tintagel Cornwall PL34 0HW United Kingdom	Intermediate 33	461	2.5
Example 108		MicroChemistry-RadaPharma Shosse Entusiastov 56 Moscow, 111123 Russia	Intermediate 33	390	2.28
Example 109		MicroChemistry-RadaPharma Shosse Entusiastov 56 Moscow, 111123 Russia	Intermediate 33	387	2.13
Example 110		Bulletin des Societes Chimiques Belges (1982), 91(2), 153	Intermediate 33	382	1.98
Example 111		MicroChemistry-RadaPharma Shosse Entusiastov 56	Intermediate 33	401	2.14

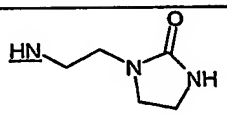
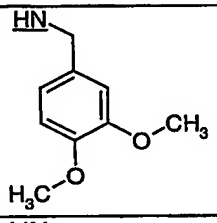
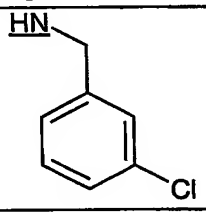
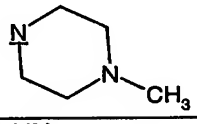
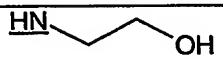
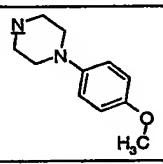
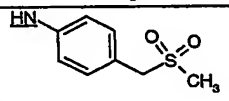
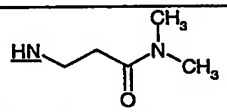
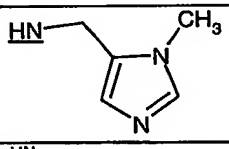
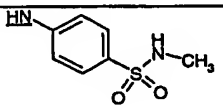
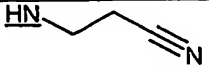
		Moscow, 111123 Russia			
Example 112			Intermediate 33	466	2.67
Example 113			Intermediate 33	425	2
Example 114		Austin Chemical Company, Inc. 1565 Barclay Blvd. Buffalo Grove, IL, 60089 USA	Intermediate 33	382	2
Example 115		WO 02/83624	Intermediate 33	464	1.97
Example 116		Fluka Chemie AG	Intermediate 33	432	2.52
Example 117		MicroChemistry- RadaPharma Shosse Entusiastov 56 Moscow, 111123 Russia	Intermediate 33	397	1.96
Example 118		WO 02/85860	Intermediate 33	423	2.09
Example 118A			Intermediate 33		
Example 119		Butt Park Ltd. Braysdown Works Peasedown St. John Bath, BA2 8LL, United Kingdom	Intermediate 33	423	2.19
Example 120		Sigma	Intermediate 33	398	1.77
Example 121		US 4562184	Intermediate 33	452	2.21
Example 122		Dynamit Nobel GmbH, Germany	Intermediate 33	372	1.93

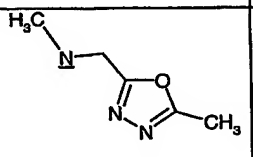
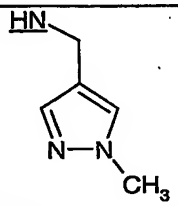
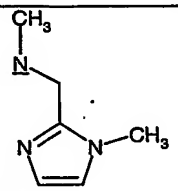
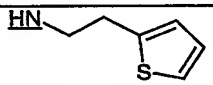
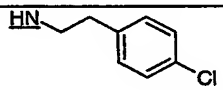
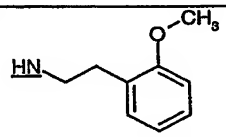
Example 123		WO 02/66470	Intermediate 33	385	1.93
Example 124		J. Med. Chem., 1990, 33(1), 97	Intermediate 33	447	2.17
Example 125		Aldrich	Intermediate 33	434	2.84
Example 126		AstaTech, Inc. 8301 Torresdale Ave. Philadelphia, PA, 19136 USA	Intermediate 33	473	2.5
Example 127			Intermediate 33	425	1.99
Example 128		J. Org. Chem., 2001, 66(6), 1999	Intermediate 33	423	1.97
Example 129		Acros Organics	Intermediate 33	401	1.82
Example 130		Aldrich	Intermediate 33	374	2.08
Example 131		Combi-Blocks Inc., 7949 Silverton Av., Suite 915 San Diego, USA	Intermediate 33	374	2.04
Example 132		J. Org. Chem., 1955, 20, 1657	Intermediate 33	487	2.39
Example 133		J. Med. Chem., 1999, 42(14), 2504	Intermediate 33	473	2.24

Example 134		Tetrahedron, 1992, 48(29), 6161	Intermediate 33	401	1.97
Example 135		Aldrich	Intermediate 33	396	2.42
Example 136		Aldrich	Intermediate 33	415	2.03
Example 137		Aldrich	Intermediate 33	401	1.78
Example 138		Aldrich	Intermediate 33	381	1.81
Example 139		MicroChemistry-RadaPharma Shosse Entusiastov 56 Moscow, 111123 Russia	Intermediate 33	387	1.74
Example 140		Aldrich	Intermediate 33	360	2.16
Example 141		Aldrich	Intermediate 33	401	1.81
Example 142		Aldrich	Intermediate 33	417	1.75
Example 143		Aldrich	Intermediate 33	376	2.16
Example 144		Aldrich	Intermediate 33	386	2.59
Example 145		Aldrich	Intermediate 33	375	1.73

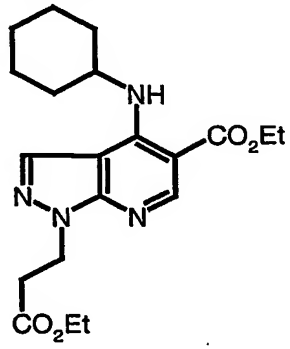
Example 146		Fluorochem Ltd. Wesley Street Old Glossop Derbyshire SK13 7RY United Kingdom	Intermediate 33	360	2.16
Example 147		Aldrich	Intermediate 33	410	2.4
Example 148		Berk Univar plc Berk House P.O.Box 56 Basing View Basingstoke Hants RG21 2E6, United Kingdom	Intermediate 33	473	2.26
Example 149		Aldrich	Intermediate 33	375	1.9
Example 150		MicroChemistry- RadaPharma Shosse Entusiastov 56 Moscow, 111123 Russia	Intermediate 33	411	1.95
Example 151		Array Biopharma Inc. 1885 33rd Street Boulder, CO 80301 USA	Intermediate 33	395	1.73
Example 152			Intermediate 33	453	1.96
Example 153		Aldrich	Intermediate 33	408	2.35
Example 154		Aldrich	Intermediate 33	416	2.5

Example 155		Aldrich	Intermediate 33	448	2.68
Example 156		Alfa Aesar, A Johnson Matthey Company 30 Bond Street Ward Hill, MA 01835-8099 USA	Intermediate 33	360	2.16
Example 157		Aldrich	Intermediate 33	330	2.04
Example 158		Aldrich	Intermediate 33	347	1.83
Example 159		Aldrich	Intermediate 33	396	2.49
Example 160		Aldrich	Intermediate 33	416	2.53
Example 161		Aldrich	Intermediate 33	390	2.18
Example 162		Aldrich	Intermediate 33	463	1.96
Example 163		US 4987132	Intermediate 33	458	2.13
Example 164		Aldrich	Intermediate 33	374	2.22
Example 165		Aldrich	Intermediate 33	406	2.53

Example 166		Maybridge Chemical Company Ltd. Trevillett Tintagel Cornwall PL34 0HW United Kingdom	Intermediate 33	402	1.93
Example 167		Aldrich	Intermediate 33	440	2.3
Example 168		Aldrich	Intermediate 33	414	2.58
Example 169		Aldrich	Intermediate 33	373	1.64
Example 170		Aldrich	Intermediate 33	334	1.85
Example 171		Aldrich	Intermediate 33	465	2.29
Example 172		EP 666258	Intermediate 33	458	2.25
Example 173		J. Chem. Soc., 1954, 1171	Intermediate 33	389	1.98
Example 174			Intermediate 33	384	1.76
Example 175		Fluorochem Ltd. Wesley Street Old Glossop Derbyshire SK13 7RY United Kingdom	Intermediate 33	459	2.36
Example 176		Lancaster Synthesis Ltd, United Kingdom	Intermediate 33	343	2.01

Example 177			Intermediate 33	400	1.92
Example 178		TimTec, Inc. P O Box 8941 Newark, DE, 19714-8941 USA	Intermediate 33	384	2.03
Example 179			Intermediate 33	398	1.70
Example 180		Aldrich	Intermediate 33	400	2.41
Example 181		Aldrich	Intermediate 33	428	2.61
Example 182		Aldrich	Intermediate 33	424	2.49

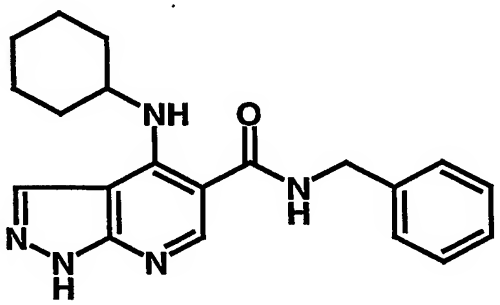
Example 183: Ethyl 4-(cyclohexylamino)-1-(3-ethoxy-3-oxopropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A vigorously stirred mixture of Intermediate 48 (40mg), anhydrous potassium carbonate (57mg) and ethyl 3-bromopropanoate (0.027ml) in anhydrous DMF (1ml) was heated at 65 °C overnight. The reaction mixture was concentrated, and the residue was partitioned between dichloromethane (5ml) and water (5ml). The phases were separated and the

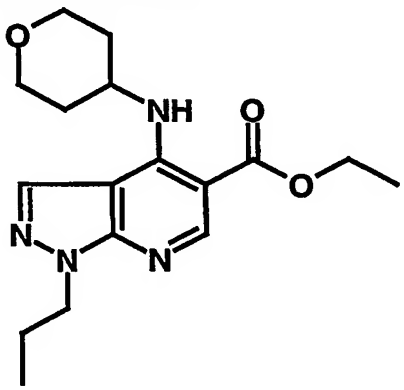
organic phase was evaporated to a residual oil which was purified by mass directed autoprep HPLC to afford Example 183 (5mg). LCMS showed $MH^+ = 389$; $T_{RET} = 3.65$min.

Example 184: ***N*-Benzyl-4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



Benzylamine (0.16ml) was added to a stirred mixture of Intermediate 49 (0.13g), DIPEA (0.26ml) and HATU (0.285g) in DMF (3ml). The resultant mixture was heated with stirring at 85 °C for 16 hours. Further portions of HATU (0.14g), DIPEA (0.13ml) and benzylamine (0.082ml) were added and the mixture heated for 16 hours at 88 °C. The resultant solution was concentrated, diluted with dichloromethane (20ml) and washed with saturated sodium bicarbonate solution (20ml), separated by hydrophobic frit and the organic layer concentrated. The residue was purified on a SPE cartridge (silica, 20g) eluting with 60-80% ethyl acetate in cyclohexane. The residue was purified further on a SPE cartridge (Isolute SCX sulphonic acid cartridge, 5g x2), eluting with methanol (2x20ml) and 10% ammonia in methanol (4x20ml); the basic fractions were combined and concentrated to give Example 184 as a white solid (0.07g). LCMS showed $MH^+ = 350$; $T_{RET} = 2.99$min.

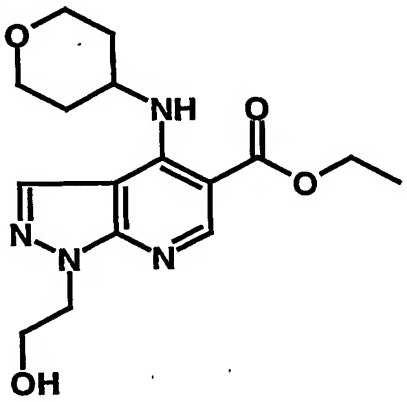
Example 185: **Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



Sodium hydride (0.067g, 60% dispersion in oil) was added to a stirred solution of Example 20 (0.47g) in DMF (19ml), followed by n-propyl iodide (0.17ml). The mixture was stirred at 23 °C for 16 hours, then concentrated, diluted with chloroform (30ml) and washed with 1:1 water:brine solution (30ml), separated and the organic layer

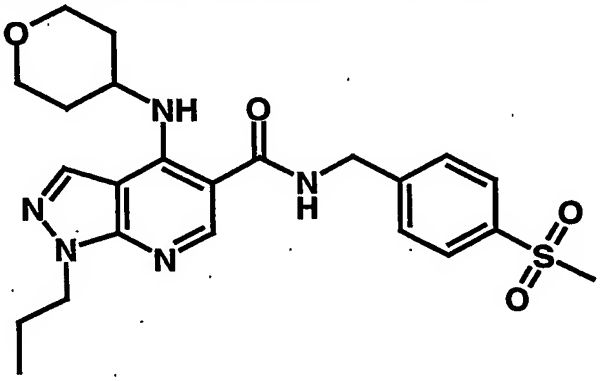
concentrated. The residue was purified on a SPE catridge (silica, 10g) eluting with 10ml volumes of dichloromethane, 1:1 diethyl ether:cyclohexane, and diethyl ether. The combined 1:1 diethyl ether: cyclohexane, and diethyl ether, fractions were concentrated to give Example 185 as a clear gum (0.23g). LCMS showed $MH^+ = 333$; $T_{RET} = 3.14$min.

Example 186: **Ethyl 1-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



2-Bromoethanol (0.008ml) was added to a solution of Example 20 (0.03g) in anhydrous DMF (1.5ml), with 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (polymer bound, 2.3mmol/g loading, 0.045g). The mixture was shaken at 23 °C for 16 hours, then the solution drained from the resin, and the resin was washed with DMF. The combined organics were concentrated, and the residue purified on a SPE cartridge (silica, 1g) eluting with 70-100% ethyl acetate in cyclohexane. The combined fractions were concentrated to give Example 186 as a white solid (0.011g). LCMS showed $MH^+ = 335$; $T_{RET} = 2.47$min.

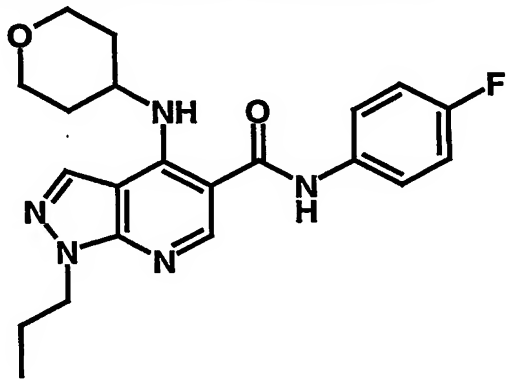
Example 187: ***N*-[4-(Methylsulfonyl)benzyl]-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



Intermediate 50 (0.03g) was stirred in DMF (1ml) with DIPEA (0.035ml) and HATU (0.038g) for 20 min. 4-(Methylsulfonyl)benzylamine hydrochloride (0.024g) was added to the mixture and the solution was stirred for 8 hours at 23 °C. The solution was concentrated and the residue dissolved in dichloromethane (6ml) then washed with saturated sodium bicarbonate solution (6ml) and 1:1 brine:water (6ml), separated by

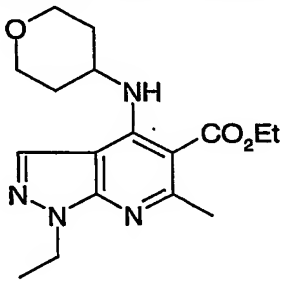
hydrophobic frit. The organic layer was concentrated to give Example 187 as a white solid (0.039g). LCMS showed $MH^+ = 472$; $T_{RET} = 2.67$min.

Example 188: ***N*-(4-Fluorophenyl)-1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



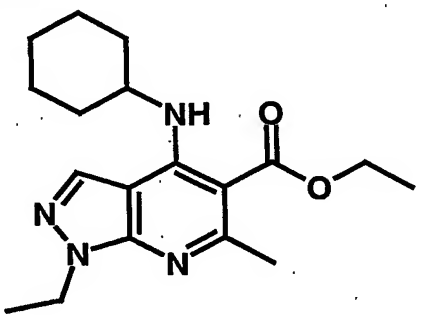
The synthetic method is as described in Example 187, except that in place of 4-(methylsulfonyl)benzylamine hydrochloride, 4-fluoroaniline (0.01ml) was added to the mixture. The resultant product required further purification, which was performed by mass directed autoprep HPLC, giving Example 188 as a clear gum (0.03g). LCMS showed $MH^+ = 398$; $T_{RET} = 3.13$min.

Example 189: **Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



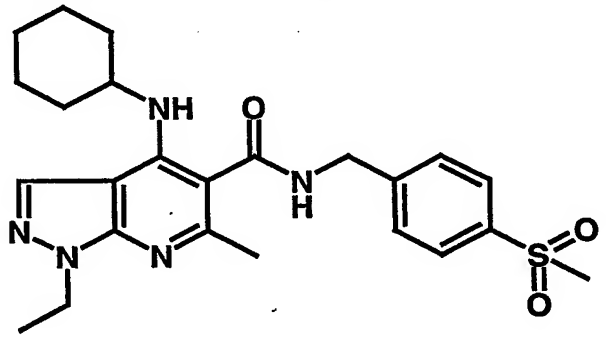
4-Aminotetrahydropyran hydrochloride (Intermediate 8A, 0.413g, 3.0mmol) was added to a mixture of Intermediate 51 (0.268g, 1.0mmol) and N,N-diisopropylethylamine (0.87ml, 5.0mmol) in acetonitrile (3ml). The resulting mixture was heated at 85 °C for 24 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and EtOAc-MeOH (9/1). Fractions containing the desired product were combined and concentrated *in vacuo* to give the desired product contaminated with starting material (Intermediate 51). Further purification using a SPE cartridge (silica, 5g) eluting with ethyl acetate-cyclohexane (1/3) afforded Example 189 (0.248g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.75$min.

Example 190: **Ethyl 4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



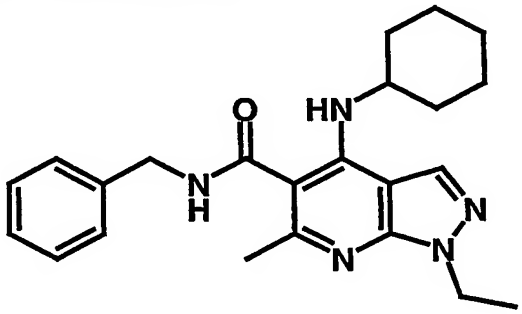
Cyclohexylamine (0.149g, 1.5mmol) was added to a mixture of Intermediate 51 (0.201g, 0.75mmol) and N,N-diisopropylethylamine (0.65ml, 3.73mmol) in acetonitrile (3ml). The resulting mixture was heated at 85 °C for 40 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and MeOH. Fractions containing the desired product were combined and concentrated *in vacuo* to afford Example 190 (0.128g). LCMS showed $MH^+ = 331$; $T_{RET} = 3.64$min.

Example 191: **4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



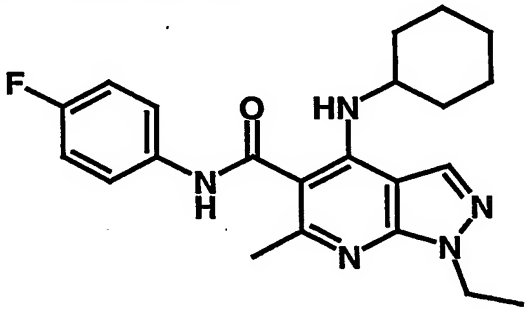
A mixture of Intermediate 52 (0.014g, 0.046mmol), HATU (0.018g, 0.048mmol) and DIPEA (0.022ml, 0.125mmol) in DMF (1ml) was shaken at room temperature for 10min. 1-[4-(Methylsulfonyl)phenyl]methanamine (0.009g, 0.046mmol) was then added, and the mixture was shaken for several minutes to give a solution. This solution was stored at room temperature for 16 hours. The solution was concentrated *in vacuo*, and the residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc-MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* to afford Example 191 (0.005g). LCMS showed $MH^+ = 470$; $T_{RET} = 2.54$min.

Example 192: ***N*-Benzyl-4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



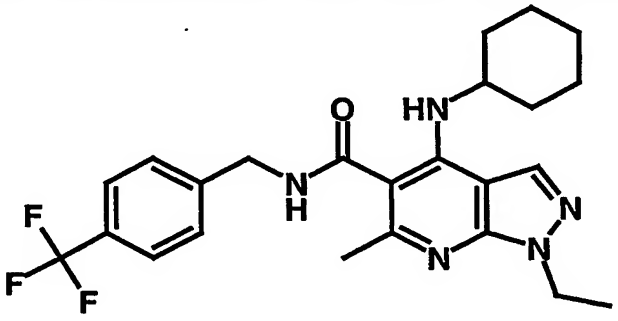
Example 192 was prepared from Intermediate 52 using a method analagous to Example 191. LCMS showed $MH^+ = 392$: $T_{RET} = 2.43$.

Example 193: **4-(Cyclohexylamino)-1-ethyl-*N*-(4-fluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



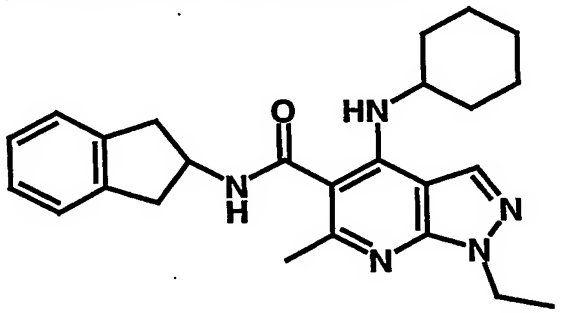
Example 193 was prepared from Intermediate 52 using an analagous method to Example 191. LCMS showed $MH^+ = 396$; $T_{RET} = 2.6$min.

Example 194: **4-(Cyclohexylamino)-1-ethyl-6-methyl-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



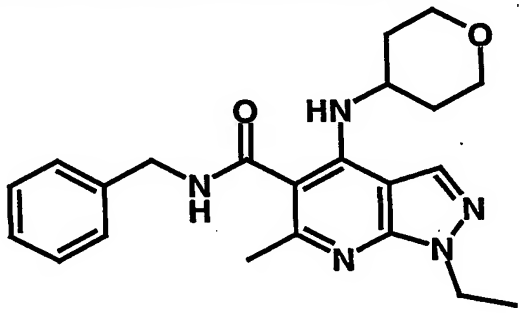
Example 194 was prepared from Intermediate 52 using an analagous method to Example 191. LCMS showed $MH^+ = 460$; $T_{RET} = 2.74$min.

Example 195: **4-(Cyclohexylamino)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



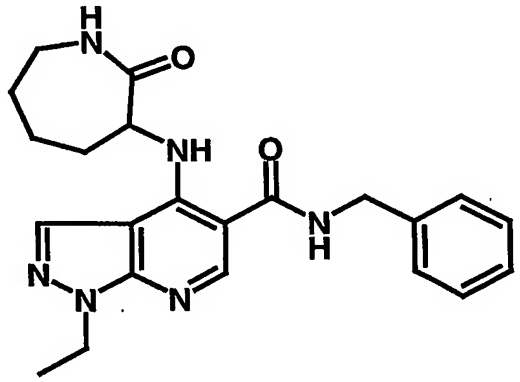
Example 195 was prepared from Intermediate 52 using an analagous method to Example 191. LCMS showed $MH^+ = 418$; $T_{RET} = 2.55$min.

Example 196: ***N*-Benzyl-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



Example 196 was prepared from Intermediate 53 using an analagous method to Example 191. LCMS showed $MH^+ = 394$; $T_{RET} = 2.02$min.

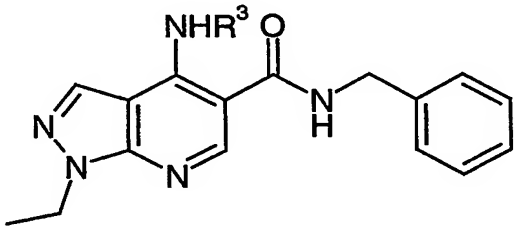
Example 197: ***N*-Benzyl-1-ethyl-4-[(2-oxoazepan-3-yl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**

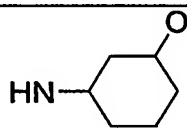
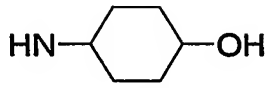
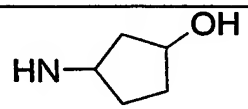


3-Aminoazepan-2-one (0.043g, 0.335mmol, commercially available from Sigma-Aldrich Company Ltd) was added to a mixture of Intermediate 17 (0.021g, 0.067mmol) and DIPEA (0.058ml, 0.335mmol) in acetonitrile (0.5ml). The resulting mixture was heated at

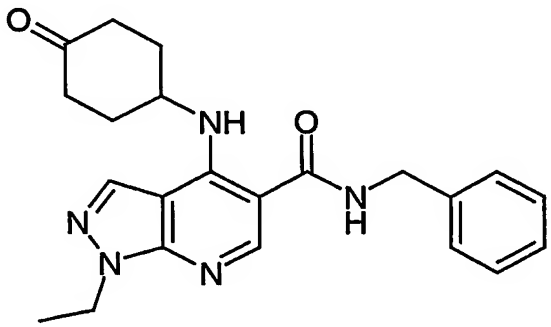
85 °C for 48 hours. Volatiles were removed in vacuo, and the residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (silica, 0.5g) which was eluted successively with diethyl ether (1.5ml), ethyl acetate (1.5ml) and ethyl acetate-methanol (9/1, 1.5ml). Fractions containing the desired material were concentrated in vacuo to afford Example 197 (0.009g). LCMS showed $MH^+ = 407$; $T_{RET} = 2.81$min.

Similarly prepared, but replacing the 3-aminoazepan-2-one with the same or similar number of moles of another amine R^3NH_2 were the following compounds:



Example Number	NHR^3	Source of R^3NH_2	Starting Material	MH^+ ion	T_{RET} (min)
Example 198			Intermediate 17	394	2.75
Example 199		Aldrich	Intermediate 17	394	2.82
Example 200			Intermediate 17	380	2.70

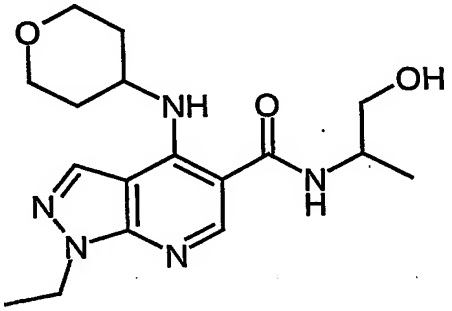
Example 201: *N*-Benzyl-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide



Intermediate 54 (0.048g, 0.32mmol) was added to a mixture of Intermediate 17 (0.050g, 0.16mmol) and DIPEA (0.17ml, 0.98mmol) in acetonitrile (3ml). The resulting mixture

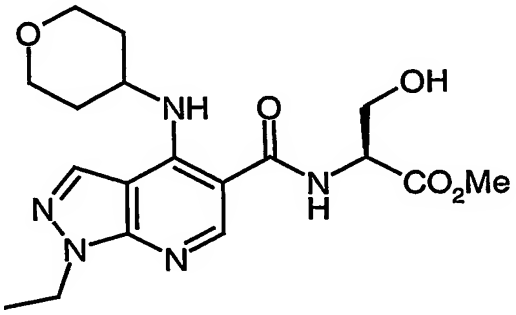
was heated under reflux. After 12 hours, further quantities of Intermediate 54 (0.044g, 0.29mmol), DIPEA (0.17ml, 0.98mmol) and acetonitrile (1ml) were added to reaction mixture which was maintained under reflux. After 36 hours, the reaction mixture was concentated in vacuo, and the residual oil was dissolved in dichloromethane (8ml) and washed with 5% sodium bicarbonate solution (2ml). Evaporation of the organic solution gave a viscous oil which was dissolved in dichloromethane (2ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with a gradient of ethyl acetate-cyclohexane (1:16, then 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing the desired material were concentrated in vacuo to afford Example 201 (0.018g). LCMS showed $MH^+ = 392$; $T_{RET} = 2.95$min.

Example 202: 1-Ethyl-*N*-(2-hydroxy-1-methylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

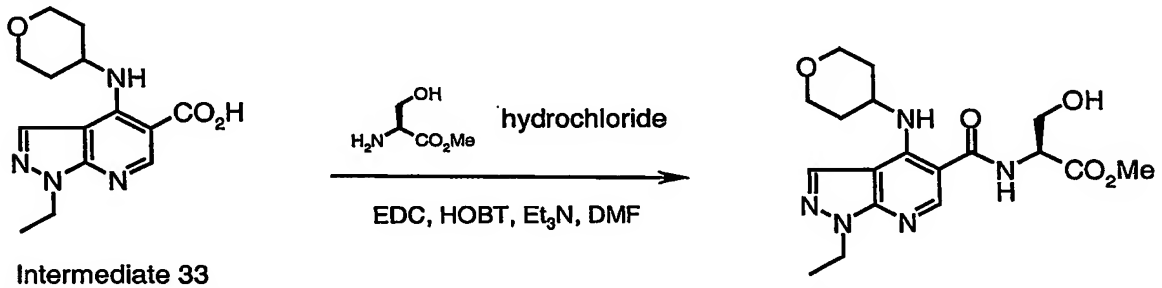


Intermediate 33 (0.1g, 0.34mmol), EDC (0.066g, 0.34mmol) and HOBT (0.05g, 0.37mmol) were suspended in DMF (2ml) and stirred at room temperature under nitrogen for 15 min. 2-aminopropan-1-ol (0.026g, 0.34mmol) and triethylamine (0.036g, 0.36mmol) were added and the mixture was stirred at room temperature under nitrogen for 6 hours. Solvents were removed in vacuo and the residue partitioned between DCM and water. The organic layer was concentrated and applied to an SPE cartridge (aminopropyl, 5g), which was eluted with methanol. Concentration in vacuo afforded Example 202 (0.095g). LCMS showed $MH^+ = 348$, $T_{RET} = 2.15$min.

Example 203: Methyl (2*S*)-2-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-hydroxypropanoate



Reaction scheme:



Intermediate 33

Intermediate 33 (0.1g, 0.34mmol), EDC (0.066g, 0.34mmol) and HOBT (0.05g, 0.37mmol) were suspended in DMF (2ml) and stirred at room temperature under nitrogen for 15 mins. L-Serine methyl ester hydrochloride (0.054g, 0.34mmol) and triethylamine (0.036g, 0.36mmol) were added and the mixture stirred at room temperature under nitrogen for 18 hours. Solvents were removed in vacuo and the residue was partitioned between DCM and water. The organic layer was concentrated in vacuo and applied to an SPE cartridge (aminopropyl, 5g), which was eluted with methanol. Concentration in vacuo afforded an impure residue which was further purified by SPE cartridge (silica, 5g), eluting with ethyl acetate followed by 5% methanol/ethyl acetate. The desired fractions were concentrated in vacuo to afford Example 203 (0.055g). LCMS showed $MH^+ = 393$; $T_{RET} = 2.22$min.